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THE POSTOPERATIVE MANAGEMENT OF PYLORIC STENOSIS *

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NEW YORK

The exhaustive work and intensive studies made in the last decade on the subject of pyloric stenosis has been productive of an almost complete understanding of the disease. The age and sex incidence is typical, the symptom complex is unusually constant, the differential diagnosis affords few difficulties and the treatment is limited practically to one procedure. There is a growing conviction that early surgical intervention is to be advised, except in a very small percentage of the cases. The etiology of the disease alone is shrouded in obscurity. Dr. Holt's paper, read before the New York Academy of Medicine in April, 1914, covered the subject from a medical point of view, and to Dr. William A. Downes should be given credit for the most complete discussion of the surgical treatment, his latest paper having been recently read before the Southern Surgical and Gynecological Congress at Cincinnati. The opportunity at the Babies' Hospital for the study of this disease may be understood when one considers the fact that in the last four years there have been admitted to the wards of the hospital seventy-five cases of true pyloric stenosis.

To the average surgeon who is called on to relieve the condition, the operation itself has few terrors, but to him, and to the practicing physician who has not been fortunate enough to see these cases, the postoperative treatment is full of difficulties. It is true that in the majority the convalescence after operation is attended by few mishaps, and this is natural when one considers the fact that there has been no impairment of the digestive functions other than that caused by starvation. A certain proportion of the patients, however, turn out to be difficult feeding problems, in spite of the fact that every facility is at hand for their proper care.

The object of this paper is to set forth, in as comprehensive a manner as possible, the usual postoperative management of these children as it has been practiced in the Babies' Hospital, and to draw attention

* Submitted for publication Jan. 6, 1916.

to the difficulties which are likely to be encountered. The study is based on the personal observation of fifty children who were operated on in this hospital during the last two years.

Since the postoperative results are dependent to no little extent on the preoperative condition of the patient, a discussion of the methods employed to improve this condition is not out of place.

PREPARATION OF PATIENT

The maintenance of the body temperature is of paramount importance; indeed the outcome of the case may hinge on the amount of care given to this detail. The metabolic processes of these children have been in abeyance, and their subcutaneous fat has been depleted by several weeks of starvation. The facility with which they develop a subnormal temperature may be readily understood; and it has been our experience that a sudden loss of body heat has, in some instances, been the undoubted cause of collapse occurring a few hours later.

The greatest danger is in the exposure incident to the operation, and to minimize this it is advisable to encase the infant's legs and arms in nonabsorbent cotton. Layers of this are covered on one side by a sheet of gauze, and the pads thus formed are folded into the shape of cylinders closed at one end, and can be drawn up over the legs and arms. Under the pad on the operating table is placed a hot water bag which fits into the small of the back and serves the double purpose of supplying warmth and keeping the site of the operation well elevated. It can be easily slipped out, if advisable, while the abdominal wound is being closed. The temperature of the operating room should be between 75 and 80 F.

The removal from the infant's stomach, by gastric lavage, of food residue and gas accumulation is the next most important preoperative measure. It should be done just before the child is taken to the operating room. Colon irrigation is unnecessary, as the intestinal coils are as a rule empty and collapsed.

Another consideration is the administration of stimulants before operation. These should be withheld except in a very small proportion of the cases. Hypodermoclysis of normal saline may be necessary in the severely dehydrated and prostrated patients, but its use before operation is open to several objections: (1) its administration entails a certain amount of exposure; (2) the tumor formed on the back may not be absorbed in time, and therefore increases the difficulties of maintaining the proper position of the child while on the operating table; and (3) not infrequently the subcutaneous fluid works around to the ventral surface of the body and encroaches on the site of operation. It is strongly advised, therefore, to postpone its use until after the operation when its beneficial effects are much more marked.

POSTOPERATIVE MEASURES

The care of the child after operation depends to some extent on the nature of the operation performed. In this series there were thirteen gastro-enterostomies and thirty-seven plastic or Rammstedt operations, of which all but two were performed by Dr. William A. Downes. The plastic operation has many advantages over the gastro-enterostomy, and it has been one of choice in the last thirty-four cases. It is more rapid, is simpler, entails less handling of the viscera, and consequently less shock, and ensures a smoother convalescence.

Maintenance of Body Heat.—In the postoperative management the maintenance of the body temperature is, as before, of the utmost importance. The infant is wrapped in a warm blanket, or cotton jacket, and the bed is well equipped with hot water bottles.

Position.—For the first hour or two the head of the bed should be lowered. This rule was adopted in the hospital when one child, while still under the influence of the anesthetic, aspirated some mucus into its larynx, after being taken to the ward, and was resuscitated only with great difficulty. After nourishment has been commenced the head of the bed may be raised and from this time on the infant is kept in a semi-erect position. This elevation assists in the emptying of the stomach, especially in the gastro-enterostomy cases, and at the same time permits the escape of gas through the mouth.

Stimulation.—The use of excessive hypodermic stimulation after operation is to be deprecated; only one measure, namely, hypodermoclysis of normal saline or of glucose solution, is always indicated, and this may be safely used as a routine practice. The amount given depends on the size of the child, but 120 c.c. or 240 c.c. are the amounts commonly used. As its administration involves exposure of the child it is important, especially in the emaciated infant, to make sure that the temperature is not subnormal. The results obtained by the use of enteroclysis are so uncertain that its employment cannot be recommended.

Of the other stimulants, epinephrin, subcutaneously, is the most satisfactory because of the rapidity of its action. Caffein and atropin, hypodermically, are sometimes valuable, and by mouth dilute whiskey or brandy. The latter cannot be given, however, until the pharyngeal reflex has returned, but it is then of unquestionable value. At times it has seemed as though merely the act of sucking from a nipple or a medicine dropper has had a stimulating effect.

It is a matter of constant surprise how well these infants withstand the shock of the operation. Frequently they look in better condition an hour afterward than they did before, and it is possible that this is due to ether stimulation. For the first half hour the child's color is,

not infrequently, poor, the pulse may be so small that its detection is difficult and the respirations are often shallow and sobbing. These signs should not cause undue alarm as they usually disappear quickly, but the child should be very closely watched for the first hour.

The value of transfusion as a stimulant is very questionable. Of the fifty cases in this series, six were transfused. In one there had been a specific indication in the form of a postoperative hemorrhage from the wound, and the beneficial result of the blood injection was immediate and impressive. In two others, who collapsed shortly after operation, the transfusion was performed solely as a stimulating measure, but had not the slightest effect. The fourth patient was one who, following operation, made a rapid convalescence for the first week, but then developed an otitis media and a severe cellulitis of the buttocks. The digestion became impaired and the weight gradually dropped. A blood transfusion was followed by a steady rise in weight and by a distinct improvement in the infectious process. The other two transfusions were performed on patients who, after operation, developed typical marasmus. One recovered and one died, but in neither instance could any beneficial effect, except a very transitory one, be attributed to the transfusion. The conclusion that the use of transfusion is of little value as a stimulating measure may be open to some criticism in view of the small number of cases described, but the same conclusion has been reached in this hospital by the study of the results obtained by transfusion in prostrated marasmus and gastro-enteritis cases.

Temperature Reaction.—A postoperative rise in temperature is to be expected in nearly all the cases. Several factors are concerned in its production: (1) the reaction from the shock of the operation; (2) the administration of hypodermoclysis and other stimulation; (3) employment of artificial heat. The height of the reaction is usually reached in from four to eighteen hours, and then gradually returns to normal during the first thirty-six hours.

The operation of gastro-enterostomy is followed by a higher and more sustained temperature than is the plastic operation, the average highest figure in eleven cases of the former variety being 102, and in twenty-six of the latter variety 101.4. The average duration of the fever after gastro-enterostomy was thirty-three and three-tenths hours, and after the plastic operation only eighteen hours. The difference in the length of the two operations, and in the amount of handling of the viscera is possibly sufficient to explain this.

A pyrexia that persists for more than three days, or one that unexpectedly occurs after the first reactionary fever has subsided, should be investigated, as it usually indicates some complication.

No antipyretic measures are needed for this reactionary temperature, except that care should be taken not to use excesssive artificial heat.

Feeding.—This is the most important feature of the postoperative care of these infants; a slight error in judgment may precipitate a gastro-intestinal upset that is very difficult to control. It is impossible to feed all the children by the same set rule, but a general routine is of value and is applicable to the majority of cases. The aim should be, as soon as possible after operation, to start nourishment in a concentrated and readily digestible form. For this purpose there is no food that can take the place of breast milk, and every effort should be made to procure enough to tide the patient over the first week at least.

The routine at the Babies' Hospital has changed to some extent in the last two years. In the early cases of this series, which were nearly all gastro-enterostomies, nourishment in the form of dilute breast milk was begun four hours after operation; water was given either one hour before this time or one hour afterward. With the advent of the plastic operation, however, it was thought that the feeding might be begun with safety at an earlier period. As this theory proved, after trial, to be correct, the following general routine was gradually evolved:

The patient is given, an hour after operation, providing the recovery from the anesthetic has been complete, 16 c.c. of water, and an hour later 12 c.c. of breast milk mixed with 4 c.c. of water. It may be necessary at first to use a medicine dropper for the administration. The breast milk is repeated every three hours, eight feedings a day, and is alternated with the water. Both are gradually increased so that twenty-four hours after operation 16 to 24 c.c. of undiluted breast milk is being given every three hours and a similar amount of water between feedings. At the end of forty-eight hours the child is usually taking 20 to 30 c.c., and at the end of seventy-two hours 30 to 45 c.c. at a feeding. The administration of water by mouth during the first three or four days is of the greatest importance. The time required to increase the milk to meet the caloric requirements of the child has been on an average five days; in small babies three days may be sufficient, and in the well nourished as much as eight to ten days.

Nursing.—Of the fifty children, thirty-four had been nursed up to admission or shortly before, and the mothers' breasts were still secreting. As the child's subsequent condition depends on the amount of breast milk that is available, every effort should be made to stimulate the failing supply. There is no better way of accomplishing this than by giving the mother a vigorous baby to nurse four or five times a day. If this is not possible a breast pump should be used.

The mother of one child in this series had not nursed her baby for eleven days before admission, and her breasts appeared to be empty.

The stimulation of nursing coupled with attention to her general health was sufficient to so restore the flow of milk that she was prepared to nurse her own baby in ten days. She was well rewarded for her trouble, since the infant during the next seven months gained fifteen pounds.

It is wise not to defer putting the baby to the breast longer than one week after operation, or when the feeding from the bottle has been increased to about 60 c.c. This is usually on the sixth or seventh day. The nursing must be carefully supervised for the next week, the amount taken at each time being measured by weighing the baby before and after. If the quantities obtained are too small, the nursing may be supplemented by a modified milk mixture.

If it is impossible to reestablish the mother's secretion, there are two alternatives open: (1) a wet nurse, if the parents can afford it; (2) the use of modifications of cow's milk. The latter may be gradually substituted for the breast milk, beginning the substitution about the tenth or twelfth day after operation.

Bathing.—In the well-nourished children a sponge bath may be given every day until the abdominal wound is completely healed and the dressing discarded. In the poorly nourished or emaciated infants an oil rub is to be preferred until a substantial gain in weight has been recorded or until the danger of the occurrence of subnormal temperature is passed.

Vomiting.—This symptom, although it is to be expected in a certain degree in a large proportion of the patients after operation, is in some cases frequent and troublesome. It is encountered after a gastro-enterostomy more commonly than after the Rammstedt operation. Twelve gastro-enterostomy patients, who survived one week or more after the operation, vomited in the first week small amounts (4 c.c. or less) an average of 6.3 times, and large amounts 4.5 times. Following twenty-five plastic operations the average number of vomitings of small amounts was only four, and of large amounts two during the same period. Vomiting persisted during the second week in 55 per cent. of the gastro-enterostomy cases, but in only 21 per cent. of the Rammstedt variety.

The more common exciting causes of the vomiting are as follows:

1. Distention due to accumulation of gas in either the stomach or intestines.

2. Defects in the operation, such as faulty adjustment of the jejunum and stomach, or incomplete severance of the constricting muscle fibers by the plastic operation.

3. A too rapid increase of the feeding.

4. The occurrence of complications, especially general peritonitis.

Of these causes distention due to gas accumulation is by far the most frequent. If it is mainly intestinal, a colon irrigation, repeated as often as is necessary, is all that is required for relief. When the accumulation is in the stomach the head of the bed should be elevated and the child frequently raised to the upright position, to allow the free escape of the gas; in the patients who do not respond to these measures it is well to pass a soft rubber catheter into the stomach before each feeding. Lavage may be employed if the vomiting is persistent, but its use in the first two or three days after the operation of gastro-enterostomy entails not a little risk.

In discussing the causes of vomiting, which are directly related to the operation itself, it should be mentioned that in the first nineteen of the Rammstedt cases an additional incision was made in the anterior wall of the stomach through which a large sound was passed into the pylorus to ensure the patency of this passage. These patients as the result of the extra trauma to the mucous membrane, showed a greater tendency to postoperative vomiting than did the patients on whom the simple muscle-splitting operation was performed. There were in addition three children whose pyloric mucous membrane was accidentally ruptured during the division of the circular muscle fibers. The defect was closed with catgut sutures, but there remained apparently a partial occlusion of the lumen, since these patients vomited excessively for two to three weeks. All eventually made good recoveries.

Persistent vomiting, the absence of fecal movements, and the demonstration of retention of food in the stomach are very suggestive of an operative defect. The diagnosis, however, is very difficult and frequently in such cases no cause for the vomiting is discovered at necropsy. In one case was found, however, a dilatation of the proximal loop, between the pylorus and gastro-enterostomy opening, in which quantities of milk had apparently collected only to be regurgitated periodically into the stomach. Another child who vomited an average of three times a day for three weeks was found at necropsy to have a stomach the capacity of which was probably not more than 30 c.c.

The history of another case serves to illustrate a cause of persistent vomiting which, though unusual, should be kept in mind. The patient, following a simple Rammstedt operation, made uneventful progress until the third day after operation, when vomiting in small quantities commenced and gradually increased in severity. The food was reduced on two occasions from 75 c.c. to 60 c.c. with a slight amelioration of the symptoms. There were one or two fecal stools of moderate size in the twenty-four hours, but an estimation of the retention in the stomach showed that only one-half or one-third of the food was entering the intestines. It was thought the relief of the pyloric constriction had not been complete, and it was not until lavage was

commenced that the true cause of the vomiting was revealed. The stomach contained an abundance of exceedingly thick, tenacious mucus which was removed only with great difficulty through the lavage tube. This mucus had evidently accumulated in the pyloric canal occluding the lumen. With the employment of frequent washings over a period of eight days the vomiting ceased and the child made a good recovery.

Stools.—Repeated fecal evacuations are usually not seen during the first twenty-four hours. At the end of this period, therefore, it is well to give a teaspoonful of castor oil to stimulate peristalsis and remove mucus and gas. The first few stools are usually loose and green in color (or meconium-like if there has been any bleeding into the stomach). Normal breast milk stools are not seen as a rule until the fourth day after operation. After the effect of the castor oil has subsided the child should have from one to three stools a day; not infrequently, however, a diarrhea occurs. This symptom is encountered to a greater degree after a gastro-enterostomy than after the muscle-splitting procedure and constitutes one of the most serious objections to this type of operation, as viewed from the standpoint of the postoperative management. Over 50 per cent. of the patients who had a gastro-enterostomy performed developed a troublesome diarrhea, but this symptom was a feature of only 8 per cent. of the Rammstedt cases.

A too rapid increase in food, especially in those children who have been vomiting for several weeks prior to operation, is very apt to produce loose frequent stools.

The measures usually employed for the relief of acute intestinal disturbances are applicable to this condition: (1) reduction in the amount of food; (2) dilution of the food; (3) reduction of the carbohydrates, best accomplished by substituting three or four feedings of protein milk for the breast milk; (4) use of medication, such as mixtures of bismuth and paregoric.

It should be mentioned in this connection that we have come to recognize a certain group of cases showing a fairly characteristic symptom complex, namely, loss of appetite, which is a danger signal never to be disregarded, drowsiness, subcutaneous edema, and frequent loose fermentative stools. Since improvement follows a reduction of the carbohydrate content of the food, by the administration for instance of protein milk, it is rational to assume that the cause of the upset was a carbohydrate intolerance, acquired, perhaps, during the weeks of starvation previous to operation.

Urine.—Before operation the urine is usually small in amount and concentrated. In forty-two cases in which the parents' observations were reliable, a diminution or concentration was noted in twenty-six,

or 62 per cent. With the administration of water following the operation there occurs a marked increase in the output of urine. It is impossible to be sure that this concentration is never injurious; it is certainly infrequently so.

One patient in this series whose symptoms had persisted for over four weeks before admission, gave a history of having passed small amounts of concentrated urine during the previous two or three days. The child was operated on the evening of admission. Toward the end of the first twenty-four hours vomiting, fever and repeated convulsions occurred, which persisted up to the time of death four days later. During this period the urine was scanty and was found to contain, on examination, a large amount of albumin and a few casts. At necropsy a severe grade of acute exudative nephritis was discovered. There was no obvious explanation for an occurrence of the nephritis other than an irritation of the kidney by a highly concentrated urine.

Weight.—The average weight of all cases on the day of operation was 6.3 pounds. Of those patients who eventually recovered twenty showed an average initial loss in weight following operation of 3.5 ounces, the low weight being reached, on an average, the sixth day after operation. In thirteen of the cases there was no initial loss in weight. Of all the patients who recovered the average gain per diem, estimated from the low weight or operation weight, was more than 0.6 ounces.

Care of the Wound.—The dressing at operation should consist of a narrow fold of sterile gauze, which just covers the incision and is held in place by adhesive strapping; there is seldom any indication to disturb it for the next four or five days. A binder should not be used. The advantage in using a small dressing is that the least hemorrhage can be readily detected and controlled. The stitches may be removed on the sixth to the eleventh day, depending on the condition of the wound, and after this a protective pad of gauze is all that is required.

Prognosis.—The prognosis in any given case depends on the duration of the disease, the preoperative condition of the child, the nature of the operation performed and the experience of the surgeon. Of the fifty cases in this collection fourteen died—a mortality of 28 per cent. There were thirty-seven Rammstedt operations with a mortality of 27 per cent., and thirteen gastro-enterostomy operations with a mortality of 30 per cent. Eight of the children who died were moribund or collapsed on admission, and in these cases the average duration of the disease before operation was seven weeks.

Fifty per cent. of the deaths occurred in the first thirty-six hours after operation, so that, until the infant has passed through this danger period, the prognosis should be very guarded. After five days

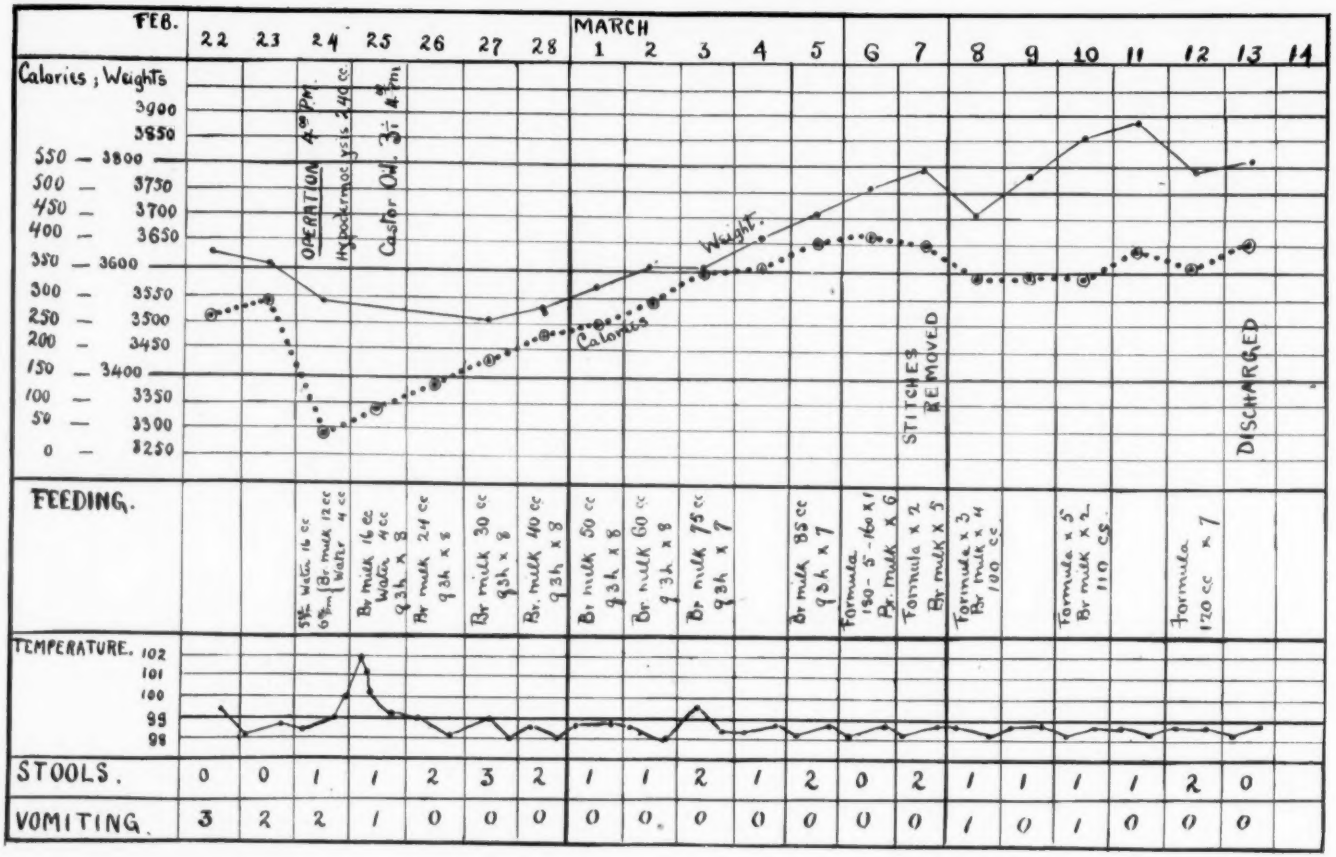

Chart showing the postoperative course of a fairly typical case. Rammstedt operation performed.

of uneventful progress the parents may be reassured as to the ultimate outcome, since serious complications, such as peritonitis or hemorrhage, are unlikely to develop later.

Causes of Death.—In only six of the fourteen fatal cases could the cause of death be definitely ascertained. One died as the result of hemorrhage into the abdominal cavity from the pyloric incision, two from general peritonitis, another from acute nephritis, and in two more death was the result of two or three weeks of persistent vomiting. The necropsy findings in the last two have already been mentioned in the section dealing with postoperative vomiting.

Of the remaining eight children, two died as the result of starvation caused by an uncontrollable gastro-intestinal upset. A necropsy in each instance revealed no pathologic change in any of the organs. Death in the other six cases was attributed to postoperative shock, but this explanation is not entirely adequate. Four, at least, showed no evidence of shock until the end of the first twenty-four hours, when collapse occurred unexpectedly. These children were all of one type, the points of resemblance being (1) a white, wrinkled, almost transparent skin, with a marked reduction of tissue turgor and other evidences of a rapid loss in weight, (2) a distinct tendency to subnormal temperature, (3) prostration to a greater or lesser degree.

It is of some interest to note that of the fourteen deaths, only three could be ascribed to medical causes; the remainder were surgical in nature.

Subsequent Course.—Of the thirty-six infants discharged in good condition, four died from a variety of causes, none of which were directly associated with the operation; the deaths occurred two weeks after discharge in two instances, and two months after discharge in the others. Two children were lost sight of, and of the remainder ten were followed for one or two years after discharge, thirteen for six months to one year, and seven for less than six months.

On the majority accurate weekly or monthly weights were obtained from the parents, and in every instance consistent gains in weight were reported. Ten children, whose weight was accurately recorded for at least nine months after leaving the hospital, gained on an average 1.3 pounds a month during this period. Eleven cases, followed for six months, at least, showed an average gain of 1.6 pounds a month. Some of the gains in weight were astonishing; two children, for instance, gained 1.5 ounces a day for four months, and several others averaged an ounce a day. The degree of improvement is naturally more striking if the baby is on the breast than it is if cow's milk is used, but in either case progress is very satisfactory.

The danger of a recurrence of the symptoms is practically negligible; a poorly executed gastro-enterostomy may be the source of trouble at a later date, but there has never been an authentic record published of a recurrence of symptoms following the Rammstedt operation.

The accompanying chart is that of a fairly typical case, and is intended to illustrate the most important incidents and treatment in the postoperative care. The solid line, which represents the weight, also represents, by striking out the last cipher, the caloric requirements of the child estimated on the basis of 100 calories per kilo. The dotted line represents the caloric intake. The steady gain in weight is interesting in view of the fact that the infant was fed its full caloric requirements only on one day—the seventh day following the operation.

I am greatly indebted to Dr. L. Emmett Holt, on whose service in the hospital these cases were observed, for permission to publish this report and also for his help in its preparation.

THE PRACTICAL VALUE OF THE GUINEA-PIG TEST FOR THE VIRULENCE OF DIPHTHERIA BACILLI

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Owing to the frequency of diphtheria and the comparative ease of making bacteriologic examinations in this disease, the laboratory has been freely used as an aid in its diagnosis and management, so that the bacteriology may be considered one of the best developed subjects in the domain of bacteriology.

The morphologic, biologic and tinctorial qualities of diphtheria bacilli are so distinctive that with comparatively little experience they are readily detected in properly made cultures, and if diphtheria bacilli were to be found on mucous membranes only in diphtheria and disappeared in a reasonable length of time after the clinical evidences of infection had disappeared, nothing would be simpler or more satisfactory than the bacteriologic diagnosis of the majority of these infections.

From a practical standpoint, however, the bacteriologic diagnosis of diphtheria is greatly complicated by reason of the fact that many persons harbor diphtheria-like bacilli in the mucous membranes, particularly of the nose and throat, that are apparently harmless and compatible with normal health. In the presence of inflammatory changes in these parts, or following direct exposures to a known case of diphtheria, the presence of these "carrier" bacilli greatly complicates the situation when it is necessary to determine whether or not a condition of infection with diphtheria bacilli may be present.

Likewise, following an attack of diphtheria, the bacilli may persist for long periods on the mucous membranes even though the patient is in all respects restored to health; most physicians have encountered these cases in private and hospital practice when prolonged, expen-

* From the Laboratory, Diphtheria and Scarlet Fever Departments of the Philadelphia Hospital for Contagious Diseases.

* Part of the paper read before the conjoint meeting of the Section of Pediatrics of the New York Academy of Medicine, the New England and Philadelphia Pediatric Societies, Philadelphia, Nov. 19, 1915.

sive and tiresome quarantine was necessary because of the possible danger of transmitting virulent bacilli to others, until repeated cultures showed the patient to be, temporarily at least, free of diphtheria bacilli.

We now know that these "carrier" cases, both the convalescent and the person who has never had clinical diphtheria, may carry either virulent and disease-producing bacilli or nonvirulent bacilli; in not a few instances both virulent and nonvirulent forms are present on the same mucous membrane. In practice it would be simplicity itself to prolong the quarantine of all convalescents until repeated cultures show the absence of diphtheria bacilli, and likewise to quarantine all healthy "carriers" who have been in contact with a person with clinical diphtheria. These procedures, however, may bring great hardship to a person or family by reason of prolonged isolation and detention; the attending physician may regard lengthy quarantine as a reflection on his ability and a reversal of his opinion regarding the condition of his patient, and he may in this manner suffer in professional reputation.

It is readily understood, therefore, that some practical and reasonably sure means of differentiating virulent from nonvirulent diphtheria bacilli is highly desirable. The test should be one that is easily applied; that is sufficiently delicate to detect the potential harmfulness of bacilli with low grade virulence and it should give the result as quickly as possible.

Before any test, however delicate and accurate it may be, can be accepted as sufficiently safe in practical work to regard a "carrier" as free of danger to himself and others on its evidence, several important questions must be answered with reasonable positiveness: 1. Can bacilli that are without disease-producing powers according to our tests resume virulence and induce disease? 2. May not bacilli of low pathogenicity produce an infection in a second individual of low resistance while causing no apparent harm to the carrier? 3. May not virulent bacilli gradually lose virulence and later resume full pathogenic powers under conditions over which we have no control?

1. Without detailing the large amount of research work by many investigators which these questions have rendered necessary, we may state that the great weight of experimental evidence is to the effect that diphtheria bacilli which have proved nonvirulent with every test, remain so indefinitely despite prolonged efforts to give them even feeble pathogenic powers. A few bacteriologists claim to have successfully accomplished this feat, but their work has not been generally confirmed.

2. It is entirely different, however, with bacilli of low pathogenicity; with these, passage through animals or from throat to throat among men, may readily enough restore a high degree of pathogenicity and for this reason any test for the virulence of diphtheria bacilli must be

one sufficiently delicate to detect the weak pathogenic powers of such cultures. It is reasonable to suppose, and clinical experience supports the contention, that a bacillus of low pathogenicity and apparently harmless to its host, may be capable of harm in a second individual.

3. The third question is more difficult to answer. Many observers have noted that diphtheria bacilli retain their virulence until they disappear, regardless of the length of their stay. We have found this to be true in not a few instances, as with patients fully recovered from diphtheria who continue to harbor virulent bacilli for prolonged periods of time. These instances are readily understood when it is remembered that diphtheria bacilli may retain their virulence for years under the more unfavorable conditions of artificial culture mediums. But in our experience we have also reason to believe that after a time, the minimum being not less than two weeks, a proportion of bacilli prove nonvirulent when tested by animal inoculation. Whether or not they regain virulence when passed from throat to throat is the important question, difficult to answer because the disease may be spread in such a varied and confusing manner, but in a considerable experience with these cases we have no direct evidence that this occurs. Most physicians depend on two or three consecutive negative cultures before discharging a patient as cured, but when one stops to consider the fallacies of this method and the goodly proportion of those who escape still carrying their bacilli, as shown by a more extended series of cultures, it is a question whether or not a good virulence test is not to be preferred.

Further than this, we have reason to believe that in some instances the prolonged number of positive cultures following diphtheria are due to the presence of harmless diphtheria-like bacilli of "carriers" that had no connection with the attack of clinical diphtheria. They were present before the attack of diphtheria and are likely to remain for an indefinite time afterward. At first they may be overgrown by the disease-producing bacilli or overlooked in cultures, but as the latter disappear the nonpathogens become prominent again and yield a formidable line of positive cultures.

It is clearly apparent, therefore, that some means of differentiating between pathogenic and nonpathogenic diphtheria bacilli must be available if the diagnosis and control of diphtheria is to be based on bacteriologic examination. Differentiation according to morphology is not usually possible or sufficiently accurate, although it is well known that the granular or beaded and barred types are more likely to be virulent than the solid types; likewise, biologic characters do not serve in this capacity; a rich creamy white growth is more frequently found with nonvirulent, solid types, while the granular, virulent bacilli grow less luxuriantly, but these characteristics are not definite. Acid production

with various sugars is likewise irregular and indefinite, although the granular, virulent types generally produce acids with dextrose and dextrin, while the nonvirulent Hoffman's bacillus produces no acid at all. Between these extremes cultures of various degrees are encountered, and indeed the variations in virulence among diphtheria bacilli have practically no parallel among other pathogenic bacteria.

The animal inoculation test therefore remains the only means now known for determining the virulence of a culture of diphtheria bacilli. To be reliable and satisfactory as a practical measure, an animal inoculation test must fulfill certain fundamental requirements:

1. It must be specific and sufficiently delicate to detect the pathogenicity of bacilli of low virulence on the basis that such bacilli may be capable of harm when transferred to the mucous membranes of persons less susceptible than the carrier.

2. The test must be simple and easily interpreted; also economical and possible of completion in as short a time as consistent with accuracy.

Aside from these requisites certain technical factors, which need not be detailed in this communication, must be considered in order to obtain the best results.

Experimental work has shown that the tissues of the guinea-pig are best adapted for conducting virulence tests, in addition to the general adaptibility of this animal for such laboratory purposes.

While there is no parallel between the mechanism of human infections and animal inoculation tests, yet experience has shown that a micro-organism found nonvirulent in a carefully conducted animal inoculation test may be regarded as harmless to human beings, although the final and decisive test is actual transference of these bacilli from throat to throat; and since diphtheria is so frequently spread in such a varied and confusing manner, absolute statements are not justifiable. As pointed out in this paper, our experience has taught us that a properly conducted virulence test may be regarded as reliable and a safe method, and much to be preferred in general, to two, or even three, consecutive negative cultures, in deciding the question of quarantine of a person harboring diphtheria bacilli over a long period of time.

In the Philadelphia Hospital for Contagious Diseases virulence tests have been conducted routinely for the past six years on cases showing positive cultures after two or three weeks' detention in the hospital, and in all cases showing diphtheria or diphtheria-like bacilli but with the diagnosis still more or less in doubt. In this class of cases are included moist or dirty noses, discharging ears or wounds, and inflamed throats showing no exudate.

Reports on the technic and results of these tests have been made by Weston and Kolmer[1] and by Kolmer.[2]

During the past two years Kolmer and Moshage[3] have made a study of various methods for determining the virulence of diphtheria bacilli, with the result that from the standpoints of delicacy and comparatively brief time required for a virulence test the subcutaneous injection into 250 to 300 gm. pigs of 4 c.c. of twenty-four-hour Loeffler culture removed with 10 c.c. of normal salt solution, yielded the best results (Table 1).

TABLE 1.—A SUMMARY OF RESULTS REGARDING THE VIRULENCE OF DIPHTHERIA BACILLI AS DETERMINED BY VARIOUS METHODS

Total Examined	Culture Medium	Hours Incubation	Route of Injection	Per Cent. Positive Results	Culture Medium	Hours Incubation	Route of Injection	Per Cent. Positive Results
37	Pl. Dext. broth	72	Subcut.	86.5	Pl. Dext. broth	72	Intracut...	64.9
23	Pl. Dext. broth	72	Subcut.	65.1	Loeffler.....	24	Subcut....	69.6
8	Serum Dext. broth	72	Subcut.	62.5	Loeffler.....	24	Subcut....	62.5
27	Pl. Dext. broth	72	Subcut.	74.0	Pl. Dext. broth	24	Intraperit.	63.0
8	Serum Dext. broth	72	Subcut.	75.0	Serum Dext. broth	24	Intraperit.	75.0
27	Pl. Dext. broth	72	Subcut.	63.0	Pl. Dext. broth	72	Intraperit.	55.5
9	Pl. Dext. broth	72	Subcut.	45.5	Pl. Dext. broth	9 days	Subcut....	66.6
8	Pl. Dext. broth	72	Subcut.	50.0	Serum Dext. broth	72	Subcut....	75.0

The subcutaneous injection of seventy-two-hour serum dextrose broth cultures in doses corresponding to the weights of the animals yielded good results but required more time for the conduct of the test; likewise the intraperitoneal injection of twenty-four-hour serum dextrose broth cultures yielded good results and had the merit of showing the result in less time than the subcutaneous method. The intracutaneous injection of 0.1 c.c. of seventy-two-hour plain dextrose broth cultures was found inferior to the subcutaneous injection of larger doses, as 1.3 c.c. for a 260 gm. pig; furthermore, the results of the intracutaneous injection were more difficult to read, especially with bacilli of a low degree of virulence. For further details and results we refer the reader to the paper mentioned.

During the past four years 1,054 virulence tests have been conducted, and the object of this paper is to report on the results observed and their practical value in the management of diphtheria.

1. Weston, P. G., and Kolmer, J. A.: Jour. Infect. Dis., 1911, viii, 295.
2. Kolmer, J. A.: Jour. Infect. Dis., 1912, xi, 56.
3. Kolmer, J. A., and Moshage, E. L.: Jour. Infect. Dis. (To be published).

TECHNIC

The technic employed in conducting the tests herein reported may be briefly described as follows:

1. Isolation of the bacilli by the "streak" method on plates of Loeffler's blood serum medium.

2. The inoculation of tubes of plain 0.2 per cent. dextrose broth with a reaction of + 0.8 with several different colonies so as to make more certain that the cultures will contain virulent bacilli if the plates contain colonies of virulent and nonvirulent bacilli.

3. Cultivation of the broth cultures at 35 to 37 C. for seventy-two hours (tubes in a slanting position so that the bacilli may receive the maximum of oxygen, which favors toxin production).

4. The examination of the broth culture for purity, followed by the subcutaneous injection in the median abdominal line of a 250 to 300 gm. pig of a dose of unfiltered culture corresponding to 0.5 per cent. of the weight of the animal expressed in cubic centimeters. The total amount injected is brought up to 4 c.c. by the addition of sterile normal salt solution in order to equalize pressure and absorption.

5. The animal is observed for at least four days for evidences of local inflammatory edema and general toxemia. If death occurs the animal is necropsied for the typical changes of diphtheritic infection, namely, local inflammatory edema, congestion of the suprarenal glands, pulmonary changes, etc. Cultures are prepared from the site of injection and the internal organs.

6. Frequently and especially when in doubt of a result and with positive or presumably virulent cultures, a second pig is injected with the same amount of culture, plus 1 c.c. of a 500-unit antitoxin serum.

7. Local edema and evidences of toxemia are regarded as indicating virulence of a culture, even though the animal does not succumb in the usual period of four days.

As will be noted, unfiltered cultures are used entirely because the soluble toxins secured by filtration are but one element of the pathogenicity of a culture, and in virulence tests it is desirable to include a test of all possible pathogenic agents.

Types of Bacilli.—In classifying the cultures submitted to the virulence test the types were recorded after the classification of Westbrook, Wilson and McDaniel. For the sake of brevity all the types found in the cultures are not recorded. For example, in a given culture of granular bacilli Types A, B and C may be found, although if one predominates, the culture is recorded according to that type. The cultures for the virulence test were recorded as follows:

A. Granular bacilli, A, B, C and D—mostly C.
B. Barred bacilli, A_1, B_1, C_1 and D_1—mostly B_1.
C. Solid bacilli:

Long solid—A_2, B_2 and C_2—mostly C_2.
Short solid—D_2 and E_2—mostly D_2.

RESULTS

The results of 1,054 tests conducted after the method outlined with granular, barred and solid bacilli from the throat, nose, ear and other mucous membranes, are shown in Tables 2, 3, 4 and 5.

TABLE 2.—Results of Virulence Tests with 551 Throat Cultures of Diphtheria Bacilli

Types	Total	Results		Per Cent. Positive
		+	—	
Granular (mostly C)	202	141	61	69.8
Barred (mostly B_1)	17	10	7	58.8
Long solid (mostly C_2)	311	144	167	46.3
Short solid (mostly D_2)	21	21	20	4.7

TABLE 3.—Results of Virulence Tests with 261 Nose Cultures of Diphtheria Bacilli

Types	Total	Results		Per Cent. Positive
		+	—	
Granular (mostly C)	102	74	28	72.5
Barred (mostly B_1)	7	5	2	71.4
Long solid (mostly C_2)	129	52	79	40.3
Short solid (mostly D_2)	23	0	23	0

TABLE 4.—Results of Virulence Tests with 217 Ear Cultures of Diphtheria Bacilli

Types	Total	Results		Per Cent. Positive
		+	—	
Granular (mostly C)	105	70	35	66.6
Barred (mostly B_1)	6	5	1	83.1
Long solid (mostly C_2)	73	31	42	42.4
Short solid (mostly D_2)	83	1	82	3.0

TABLE 5.—Results of Virulence Tests with 25 Miscellaneous Cultures of Diphtheria Bacilli

Sources	Types	Total	Results		Per Cent. Positive
			+	—	
Penis	Long and short solids	6	0	6	0
Vagina	Long solids	6	0	6	0
Eye (normal)	Long solids	4	0	4	0
Gallbladder	Long solids	1	0	1	0
Skin	Long and short solids	8	0	8	0

Table 6 is a summary of the virulence of the different types of bacilli from the different sources.

TABLE 6.—Comparative Virulence of the Different Types of Bacilli from Different Sources

Type of Bacilli	Percentage of Positive Results of Cultures			
	From Throat	From Nose	From Ear	From Various Other Sources
Granular (mostly C)	69.8	72.5	66.6	None tested.
Barred (mostly B_1)	58.8	71.4	83.2	None tested.
Long solid (mostly C_2)	46.3	40.3	42.4	0
Short solid (mostly D_2)	4.7	0	3.0	0

An examination of these tables shows the following:

1. The granular and barred types of bacilli give the highest percentage of positive tests. In clinical diphtheria they are almost invariably virulent for guinea-pigs. No matter how long they persist in the throat after recovery, they should be regarded as dangerous until proved otherwise. Of all types they are most likely to retain their virulence.

2. The value of animal inoculation tests is especially appreciable when dealing with solid types of bacilli. The longer types are more likely to retain virulence than the shorter varieties. Both, however, may be descendents of the "carrier" bacillus rather than of the bacillus producing the clinical evidences of the disease.

3. The short solid types of bacilli are especially common in the nose in the absence of clinical diphtheria. In a small percentage of cases these bacilli may be truly pathogenic but the majority of cultures are found without virulence when tested by animal inoculation.

4. The long solid types of bacilli, so frequently found in otitis media, are in the majority of cases nonvirulent.

5. Animal inoculation tests have a special field of usefulness in testing the solid types for virulence when they persist in the tissues over a long period of time or when found after contact with "carrier" cases.

6. Cultures of the short solid D_2 types have proved nonvirulent with such regularity that whenever we are sure that the type is true we do not hesitate to report negatively on the culture and release quarantine. Although this method has been in practice for several years and concerned the discharge of hundreds of cases, no return cases can be attributed to the presence of these bacilli in the throats or noses of their hosts.

The majority of the cultures tested by us were from patients who had been in the hospital for fifteen to twenty-two days, and after the disappearance of clinical evidences of the disease. A few cultures were tested in the first week of the disease, especially when the clinical evidences of diphtheria were slight or atypical.

The results of the virulence tests according to the day of disease are shown in Tables 7 and 8.

Table 7 is a summary of the positive results observed with granular or beaded bacilli from the throat, nose and ear; Table 8 is a similar summary of the positive results with the long, solid C_2 types of bacilli. The numbers of cultures tested of barred bacilli were too few to prepare a table, and the short solid B_2 types of bacilli were uniformly without virulence in these tests.

TABLE 7.—A SUMMARY OF POSITIVE VIRULENCE TESTS WITH GRANULAR DIPHTHERIA BACILLI AT VARYING INTERVALS AFTER INFECTION

Week of Disease	Percentage of Positive Virulence Tests		
	Throat	Nose	Ear
1	100	70	50
2	70	100	68.7
3	67.5	80.6	80.0
4	73.9	75.0	60.0
5	83.3	75.0	66.6
Over 5	91.0	86.6	100.0

TABLE 8.—A SUMMARY OF POSITIVE VIRULENCE TESTS WITH SOLID DIPHTHERIA BACILLI AT VARYING INTERVALS AFTER INFECTION

Week of Disease	Percentage of Positive Virulence Tests		
	Throat	Nose	Ear
1	None tested	40.0	50.0
2	68.2	14.3	14.3
3	41.7	41.3	37.5
4	51.1	42.8	30.0
5	57.1	28.5	None tested
Over 5	47.7	40.0	0

These tables are not composed of the results observed of testing the cultures of a group of patients at regular intervals, but were compiled from the 1,054 tests.

As shown in these tables, a percentage of cultures retain their virulence for indefinite periods after the disappearance of clinical evidences of infection. In other words, virulent bacilli are likely to retain their virulence for prolonged periods when tested at intervals, so that negative virulence tests are not to be expected on the basis of duration of

disease alone; in a given case the tests are likely to yield persistently positive results as long as that particular culture of diphtheria bacilli is secured in culture. As previously stated, however, in our experience a small percentage of cultures presenting the same morphology were observed to lose virulence as tested at varying intervals; it is probable, however, that the majority of negative virulence tests following previous positive results are due to the fact that the virulent bacilli have gradually disappeared or their colonies were overlooked in the cultures.

PRACTICAL VALUE OF VIRULENCE TESTS

In the handling of diphtheria, second only in importance to the prompt, vigorous and specific treatment of the disease itself is the determination of the time when the individual ceases to possess the power of infecting others. This applies to "carriers" as well as to convalescents from clinical diphtheria.

As already stated, virulence tests may serve a useful function in differentiating between virulent and nonvirulent diphtheria bacilli when the micro-organisms persist over long periods of time on the mucous membranes or in persons who carry these bacilli, either after or without contact with a clinical case of diphtheria.

For the proper management of diphtheria according to bacteriologic examinations, an effort must be made to differentiate between the harmful and harmless bacilli. For instance, a "carrier" may be quarantined forever if guided by the fact that the presence of a diphtheria-like bacillus means diphtheria. The medical attendant must be convinced of the value of bacteriologic examinations and of the earnest efforts of the bacteriologist to work with him both in the interests of his patient and for the public welfare. The practitioner must be taught not to be afraid to report all of his cases and to culture faithfully. If, however, bacteriologic examinations serve to give unnecessary embarrassment to the practitioner by quarantining "carrier" cases, or by maintaining a quarantine unnecessarily long after convalescence as a result of conscientious efforts on the part of the latter to do his duty in taking cultures, he is not likely to give his best cooperation, and without this no real good is possible.

In the Philadelphia Hospital for Contagious Diseases in all instances in which the virulence test is negative the patient is considered noninfectious and fit for release from quarantine, regardless of what the cultures may show. These cases have been followed closely and the number of "return" cases has become practically negligible. On the other hand, we have on several occasions observed that convalescent children harboring virulent bacilli as determined by animal inoculation test, but subsequently released from quarantine on the basis of two or

three negative cultures, have been responsible for the infection of others.

The results have shown quite definitely that the virulence test is the safest and nearest perfect method that has been devised, and regardless of all things else, in the face of negative pig test, the patient is discharged; in the face of a positive test he is detained.

If the physician will take cultures carefully, conscientiously and freely, especially several cultures, before excluding the diagnosis of diphtheria in a given case, and if three consecutive negative cultures are required instead of two before quarantine is lifted, combined with the efforts of the bacteriologist to differentiate between virulent and nonvirulent bacilli, with the judicious use of the animal inoculation test in suitable cases, we believe that the bacteriologic diagnosis and management of diphtheria will be efficient and satisfactory to all.

CONCLUSIONS

1. Animal inoculation tests have been found of great value in determining the virulence of diphtheria bacilli.

2. Virulence tests are the only practical and safe means of determining the possible harmfulness of diphtheria bacilli.

3. Virulence tests have been found useful in the management of diphtheria bacillus "carriers," especially from the standpoint of duration of quarantine. This applies to healthy "carriers" discovered as the result of cultures, and to convalescents and persons showing atypical or slight clinical evidences of infection of the throat, nose, eye, wounds, etc., with cultures showing the presence of diphtheria bacilli.

4. Virulence tests in order to be practical and reliable must be sufficiently delicate to detect low degrees of virulence and this constitutes the first and important essential; it is desirable to conduct the test as economically and as speedily as consistent with specificity and delicacy.

5. Subcutaneous injection of 250 to 300 gm. guinea-pigs with cultures was found to yield better results than intracutaneous and intraperitoneal injection. The subcutaneous injection of 4 c.c. of a good twenty-four-hour culture of diphtheria bacilli on a tube of Loeffler's medium washed off with 10 c.c. of normal salt solution, was found as delicate and specific in its results as any method, besides being a test requiring a short space of time for its conduct.

A second method yielding excellent results, but requiring more time, consists in cultivating the bacilli in serum dextrose broth for seventy-two hours and injecting 250 to 300 gm. pigs subcutaneously with 1.3 to 1.5 c.c. of unfiltered culture.

6. Local edema and even slight evidences of toxemia of the test animal with absence of those signs in the antitoxin control, are regarded

as indicating virulence even though the animal does not succumb in the four-day period of observation.

7. Granular types of diphtheria bacilli were found virulent in about 70 per cent. of cultures from the throat, nose and ear; barred bacilli were found of equal virulence with the granular types. Long solid bacilli were found virulent in about 42 per cent. of cultures; cultures of short solid bacilli were found uniformly to possess no virulence.

8. Virulence tests were found of most value in determining the potential harmfulness of the solid varieties of diphtheria bacilli because these types are especially likely to be found in carriers.

METHODS OF USING DIPHTHERIA TOXIN IN THE SCHICK TEST AND OF CONTROLLING THE REACTION

RESULTS OBTAINED WITH THE TEST IN 2,700 CHILDREN*

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The practical value that the Schick reaction[1] has acquired in the diagnosis of susceptibility or immunity to diphtheria makes it desirable to say a few words about the toxin used in the test, the overneutralized or the heated toxin used in the control test, about the technic of the test, and finally about the interpretation of the reactions.

The diphtheria toxin for use in the Schick test consists of a broth culture of the diphtheria bacillus, which has been grown in the thermostat at 37 C. for six days. To kill the living organisms 10 parts of a 5 per cent. solution of phenol (carbolic acid) (0.5 per cent.) are then added, and the bacteria allowed to sediment by keeping the broth culture in the ice box during the following two or three days. The supernatant culture fluid is now passed through a Berkefeld filter, and the clear filtrate of toxin standardized. This is only a preliminary standardization. Since a considerable part of the toxin is converted into toxoids during the succeeding twelve to eighteen months, we have to use, for purposes of the Schick test, a toxin that has been ripened for at least a year, and then carefully standardized by determining the M.L.D. of the toxin for a 250-gram guinea-pig. One fiftieth of the M.L.D. in 0.2 c.c. of sterile physiologic salt solution is injected intracutaneously on the flexor surface of the forearm or arm.

The undiluted diphtheria toxin can be obtained either in bulk (vials of 2 c.c.) or in the single outfits devised by me.

The bulk toxin will keep its strength very well if a ripened toxin is used. A *primary dilution* of the toxin is first made by adding 100 M.L.D. to a sufficient amount of sterile physiologic salt solution to make

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* Read before the Pediatric Section of the New York Academy of Medicine, Nov. 11, 1915.

1. Schick, B.: Spezifische Therapie der Diphtherie, Centralbl. f. Bakteriol., 1. Abt., 1913, lvii, Ref., Beiheft 16-35. Schick, B.: Die Diphtherietoxin-Hautreaktion des Menschen als Vorprobe der prophylaktischen Diphtherieheilseruminjection, München. med Wchnschr., 1913, lx, 2608.

10 c.c. For instance, if the M.L.D. of the toxin is 0.007 c.c., then 0.7 c.c of the undiluted toxin is added to 9.3 c.c. of salt solution. Each cubic centimeter of the primary dilution will represent 10 M.L.D. This primary dilution will keep in the ice box for about two weeks. For the Schick test a fresh *final dilution* is made daily, or whenever required, by drawing up with the record syringe 1.0 c.c. of the primary dilution and adding it to 99 c.c. of sterile salt solution. Several bottles of saline (99 c.c.) may be conveniently kept on hand. The final dilution represents in 1.0 c.c. 1/10 M.L.D., and in 0.2 c.c. 1/50 M.L.D., the amount injected intracutaneously in the test. This method of diluting the toxin is convenient for use in institutions, where a large number of children are to be tested at one time, or in places where the daily carrying out of the test requires that a fresh dilution of toxin be frequently prepared. If the undiluted toxin and the primary dilution are kept very cold (45 F. or less), there will be no danger of deterioration, and the results with the test will be reliable.

In view of the necessity of the general practitioner's having a more convenient way of obtaining the undiluted toxin and of diluting it with the proper amount of sterile saline, an outfit has been devised which can be obtained by physicians in New York City from the Bureau of Laboratories of the Department of Health. These outfits are also supplied by several commercial laboratories. The outfit has been described in a previous communication.[2] Owing to a slight modification the essential parts of the outfit will be given again.

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2. Zingher, Abraham: A Simple Outfit for the Distribution of Toxin for the Schick Test, Jour. Am. Med. Assn., July 24, 1915, p. 329.

In each package there is a capillary tube, which contains a little over 1 M.L.D. of ripened, undiluted diphtheria toxin; a small rubber bulb, similar to the ones used in the vaccine outfits, and a bottle, which contains 10 c.c. of sterile physiologic salt solution. To use the outfit one end of the capillary glass tube is broken off, and the end carefully pushed through the neck of the rubber bulb, until it punctures the diaphragm within, and enters the cavity of the bulb; the other end of the tube is then broken off. The bulb is now held between thumb and middle finger, the index finger placed over the opening in the larger end of the bulb and the toxin expelled into the saline. The capillary tube is rinsed out by drawing up saline several times, the bottle is corked and the diluted toxin shaken. Each cubic centimeter of the dilution represents 1/10 M.L.D., and every 0.2 c.c. 1/50 M.L.D., the amount used in the test. The capillary tubes with the toxin may also be obtained in quantities of 6 and 12. By refilling the 10 c.c. bottle with sterile salt solution or with cool boiled water, a fresh dilution can, whenever required, be readily prepared.

The undiluted toxin in the capillaries will deteriorate very little, if care is taken to keep the outfits in a very cold place. The diluted toxin should not be used after twelve to twenty-four hours. Each capillary tube contains a small excess of toxin (1¼ M.L.D.) to allow for any possible slight deterioration.

It was with the hope of popularizing a test, which has given us[3] and others[4] such reliable results, especially in children up to the age of 15 years, when pseudoreactions are relatively rare, that this outfit has been devised and made available for the general practitioner. No stronger proof of the reliability of the reaction need be offered, than the fact that of 1,000 patients sick with scarlet fever at the Willard Parker Hospital, who had given a negative test on admission, not one developed clinical diphtheria, although no antitoxin had been injected, and about 15 to 20 per cent. of the children showed, during their stay in the institution, virulent diphtheria bacilli in throat cultures.

The three prerequisites for the test are: (a) a reliable toxin, (b) a proper technic, and (c) a correct interpretation of the reaction. Care in getting and keeping the toxin will answer the first. A good syringe (preferably a 1 c.c.) and a fine, sharp, but short-beveled platinum-iridium needle are needed for the second. The ability to carry out the test properly is easily acquired. One point that may serve in guiding one in the injection of the diluted toxin might be emphasized. If the needle has been inserted into the proper layer of the epidermis, then the oval opening of the needle will be visible through the superficial layers of cells. A definite wheal-like elevation, with the distinct markings of the openings of sweat glands, shows that the injection has been made properly, and that the fluid is confined to small area of the epidermis. Here it will exert its irritant action, if the individual tested is not immune to diphtheria.

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3. Park, W. H., Zingher, Abraham, and Serota, Harry M.: The Schick Reaction and Its Practical Applications, Arch. Pediat., 1914, xxxi, 481. Park, W. H., and Zingher, Abraham; Practical Applications Obtained from the Schick Reaction, Proc. New York Path. Soc., October, 1914. Zingher, A.: The Schick Reaction and Its Practical Applications, Med. Rec., 1915, lxxxvii, 752. Overton, F., Zingher, A., and Turrell, G. H.: The Use of the Schick Test in the Suppression of a Diphtheria Outbreak, Month. Bull. New York State Dept. Health, 1914, xxx, 279.

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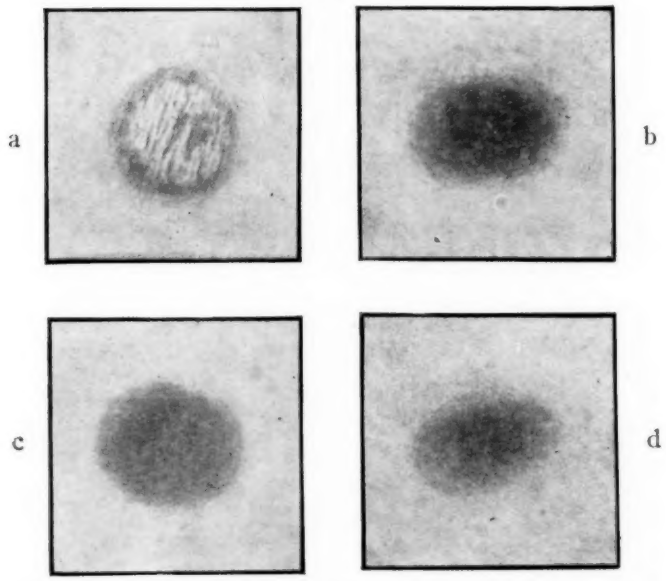
For the interpretation of the test, it is important to remember that the *positive* reaction (Plate I) represents the action of an irritant toxin on unprotected cells. A trace of redness appears slowly at the site of injection in from twelve to twenty-four hours, and usually a distinct reaction in the course of twenty-four to forty-eight hours. The reaction reaches its height on the third or fourth day and gradually disappears, leaving a definitely circumscribed scaling area of brownish pigmentation, which persists for three to six weeks. At its height the positive reaction consists of a circumscribed area of redness and slight infiltration which measures from 1 to 2.5 cm. in diameter. The degree of redness and infiltration varies to a great extent with the intensity of the reaction. In the *negative* reaction, the skin remains normal. In the *pseudoreaction* (Plate II, a, b) there is an anaphylactic response of the tissues cells to the protein substance of the autolyzed diphtheria bacilli, which is present in the toxic broth used for the test. Like other anaphylactic skin phenomena, the reaction is of an urticarial nature, appears early, within six to eighteen hours, reaches its height in thirty-six to forty-eight hours, and disappears on the third or fourth day, leaving no pigmentation or only a poorly-defined, small, brownish spot. At its height the pseudoreaction shows varying degrees of infiltration, and appears as a small central area of dusky redness, with a secondary areola, which gradually shades off into the surrounding skin. A control test may be made by injecting into the other forearm in the same dilution, diphtheria toxin which has been either heated to 75 C. for five minutes to destroy the soluble toxin, or has been overneutralized by the addition of antitoxin. This mixture is prepared by adding two units of antitoxin to each L + dose of toxin. If the first test gave a positive reaction, then the control test will be negative. If the original test was a pseudoreaction, then the control will show a similar area of redness and infiltration, and both reactions will run the same clinical course, namely, disappear in three to four days and leave little if any pigmentation behind. Since the free toxin in the solution has been either destroyed by heat or neutralized with antitoxin, the only active substances that remain are the protein of the autolyzed diphtheria bacilli and the constituents of the nutrient broth. Sterile broth in the same dilution will not as a rule give the pseudoreactions; in a lesser dilution it will show in some a faint reaction. The trace of added antitoxin (one part to a million) will not by itself show any reaction. We must, therefore, conclude that it is the protein of the autolyzed diphtheria bacilli, which is the active agent. Similar and even more intensive pseudoreactions may be obtained with a dilution of an autolysate of diphtheria bacilli, which contains no trace of soluble toxin. Overneutralized diphtheria toxin or heated toxin, for use in the control tests, can be obtained in capillaries similar to those for the Schick test.

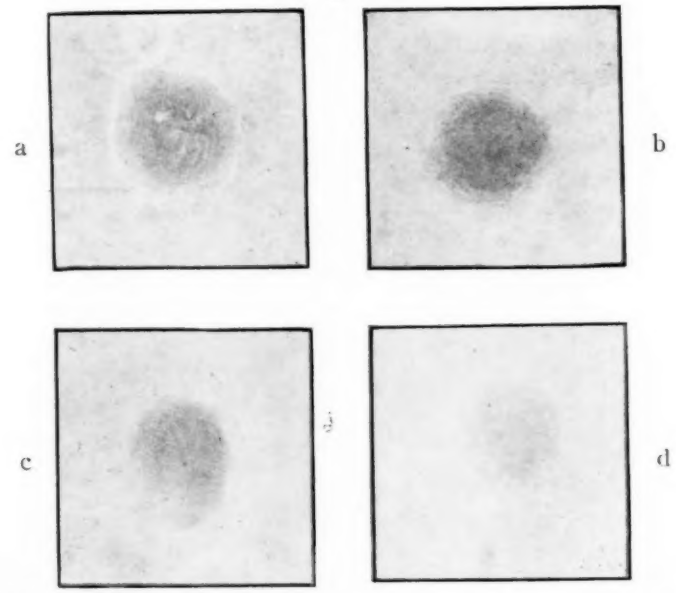
PLATE I

A



A—Shows four typical positive Schick reactions of varying degrees of intensity forty-eight hours after test; (a) is a strongly positive reaction, with vesiculation of the surface layers of the epithelium, which is seen occasionally in individuals who have practically no antitoxin; (b) and (c) are positive reactions; (d) a moderately positive reaction.

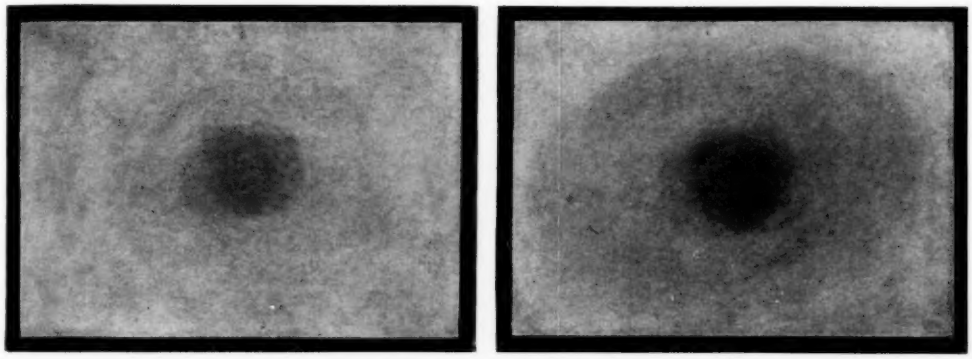
B



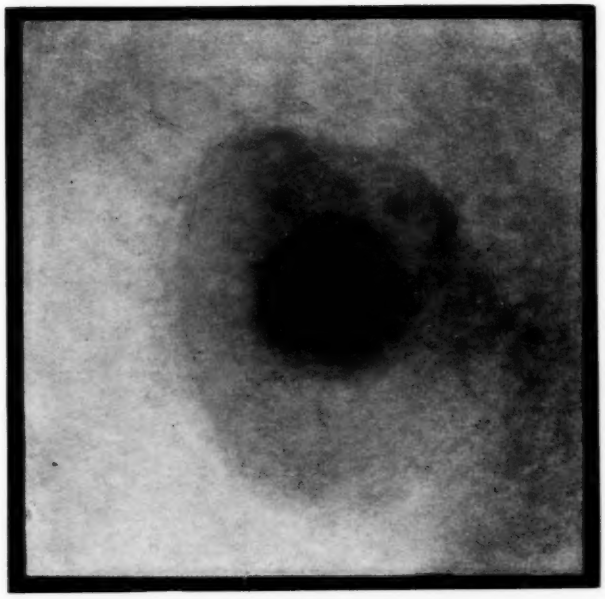
B—Shows a fading positive Schick reaction one to four weeks after test in various stages of scaling and pigmentation; (a) shows redness, scaling and beginning pigmentation after one week; (b) and (c) pigmentation after two and three weeks; (d) faint pigmentation after four weeks.

Illustrating Article by Abraham Zingher, M.D., American Journal of Diseases of Children, April, 1916.

PLATE II



a b



c

Shows two pseudoreactions forty-eight hours after test, and a combined reaction; (a) mild; (b) marked; (c) a combined positive and pseudoreaction.

Occasionally one sees a *combined reaction* (Plate II, c) which represents both a positive and a pseudoreaction. The central area of redness is larger and better defined; the amount of infiltration is also more marked. To interpret such a reaction we should obtain the evidence of a true reaction, a definite area of scaling brownish pigmentation after the pseudo element has disappeared in the test. In addition, we should obtain a similar, though weaker reaction in the control test made with heated or overneutralized toxin. The control will, of course, represent only the pseudoreaction. These pseudoreactions are rarely seen in the young, but quite frequently in the adult. Unless one is able carefully to differentiate them from the positive reactions it will be safer in practice to consider all reactions as positive, and treat them as such on exposure to diphtheria.

For purposes of recording the tests we may designate the positive reaction by the following signs, which represent varying degrees of intensity. This is especially important in the active immunization with mixtures of diphtheria toxin and antitoxin when we wish to know the degree of the original or control test before the immunizing injections, and of tests made at intervals after the injections.

++ strongly positive. Marked redness and considerable local infiltration, occasionally superficial vesiculation.
+ positive. Redness and little or no local infiltration.
± moderately positive. Varying degrees of redness and no local infiltration.
± faintly positive. Slight redness and no local infiltration.
— negative. No redness and no local infiltration.

Several groups of healthy children were tested with the Schick reaction and the results shown in the accompanying table obtained:

SUMMARY OF SCHICK TESTS FROM THREE LARGE ORPHAN ASYLUMS (NORMAL CHILDREN)

Age Years	Total	— Schick	+ Schick	Per Cent. + Schick
2- 4	62	42	20	32.2
4- 6	318	236	82	25.7
6- 8	444	347	97	21.8
8-10	597	462	135	22.6
10-12	584	459	125	21.4
12-14	506	416	90	17.7
14-16	189	158	31	16.4
	2,700	2,120	580	21.4

It is rather important to note in our table of normal children, that not more than 17 to 32 per cent. of children between the ages of 2 and 14 years gave a positive reaction. This is a significant factor in the active immunization against diphtheria with mixtures of toxin-

antitoxin, since the relatively small number of individuals that need to be protected makes the work, from the ease with which it could be accomplished, of distinct practical value. In some 1,200 children suffering with scarlet fever we had found a larger proportion (65 per cent.) of positive reactions between the ages of 2 and 6 years. This is possibly due to the fact that the higher temperature of scarlet fever with the associated increased metabolism of the body causes a breaking down of the trace of natural antitoxin, which is just sufficient to give a negative reaction in some of the healthy children; possibly, also, those who are susceptible to scarlet fever are more apt to be susceptible to diphtheria, that is, give a positive Schick reaction.

Combined reactions were noted among the reactors in this group in about 10 per cent. of the older children, especially among the females; a smaller proportion of the children showed pseudoreactions.

The testing of large numbers of children can be easily accomplished, if the children are standing in line and their forearms have been exposed and cleaned with alcohol. With a properly working syringe and needle, each operator can make as many as 200 to 250 tests an hour, the needle being rapidly cleaned between the injections with a cotton sponge saturated with alcohol. The children should be seen at the end of twenty-four hours to determine the presence of the pseudo and combined reactions; they should be seen again in forty-eight and seventy-two hours. Careful notes should be kept of the character of the reactions, and the pseudoreactions should be controlled, for the sake of accuracy and experience, with the heated or overneutralized toxin. Individuals who give a pseudo or a combined reaction are much more susceptible to the local action of antitoxic serum, or of immunizing injections of toxin-antitoxin serum.

The testing of children on a large scale in schools and institutions can be thus readily accomplished and a permanent record kept of the reactions. From the results which we have obtained in the testing of older children and adults we feel fairly certain that the majority of children who have reached school age and show a negative reaction, are protected for years and probably for life.

The data that we thus obtain will represent valuable facts both for the individual and for the community. For the individual the assurance of an immunity to diphtheria will save many an hour of worry over repeated attacks of catarrhal laryngitis, or a suspicious tonsillar exudate in which possibly a positive bacteriologic examination has been made. For the community we may, with an increasing knowledge of the number of permanent immunes, and the careful study of the transition periods of the susceptible individuals to a stage of immunity, as well

as the carrying out of an active immunization[5] of the susceptible ones, be finally able to control a disease which continues to be one of the big issues of preventive medicine. The failure so far has been made especially evident by our attempts to deal with the problem of the bacillus carrier. It will probably not be by the elimination of the bacillus carriers, but rather by the active and possibly permanent immunization of the susceptible individuals in a community that we will prevent fresh cases of infection and, to some extent at least, the development of new foci for the dissemination of virulent diphtheria bacilli.

CONCLUSIONS

1. The great practical value connected with the Schick test makes it desirable that the results obtained with it should be reliable.

2. The accuracy of the results will depend not only on the toxin, but also on the care with which the test is made, and on the interpretation of the reaction.

3. The undiluted toxin is available in bulk or in capillary tubes. It should be well ripened and always kept very cold and in a dark place.

4. The positive reaction should be considered as indicating a lack of immunity, unless the pseudoreaction can be eliminated by a control test. The negative reaction is a definite sign of immunity.

5. It is important to remember that, in using diphtheria toxin in the Schick test, we are dealing with an accurate quantitative reaction, and handling carefully measured amounts of an active agent, that has a tendency to deteriorate, even in bulk, if it is not properly protected from light and exposure, and kept in a very cold place.

6. The results with the test obtained in 2,700 normal children, show that from 17 to 32 per cent. between the ages of 2 and 16 years give a positive reaction and are probably susceptible to diphtheria.

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5. Von Behring: Ueber ein neues Diphtherieschutzmittel, Deutsch. med. Wchnschr., 1913, xxxix, No. 19. Park, W. H., Zingher, Abraham, and Serota, Harry M.: Active Immunization in Diphtheria and Treatment by Toxin-Antitoxin, Jour. Am. Med. Assn., Sept. 5, 1914, p. 859. Park, W. H., and Zingher, Abraham: Active Immunization with Diphtheria Toxin-Antitoxin, and with Toxin-Antitoxin Combined with Diphtheria Bacilli, Jour. Am. Med. Assn., Dec. 18, 1915.

D'ESPINE'S SIGN IN CHILDHOOD*

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This study was undertaken because of the difference of opinion which prevails as to what constitutes D'Espine's sign, and because of my impressions that D'Espine's sign is much less often present in the children of the well-to-do than in those of the hospital class, and that, when present in children of this class, it is in a considerable proportion of the cases not a manifestation of tuberculous infection. Six hundred and sixty-six patients, seen in my consultation and office practice during the last three years, form the basis of this study. These children were consecutive, except when for some reason they were unable, or unwilling, to talk, or when, through some oversight, a test was either not made or no record kept of it. The sign was tried for simply as part of the routine physical examination, and at the time the tests were made I had no intention of using the results for any purpose. The conclusions derived from these results, therefore, should be entirely unbiased.

Professor Adolphe D'Espine of Geneva in an article on "The Early Diagnosis of Tuberculosis of the Bronchial Glands in Children,"[1] said that he had called attention briefly to this method of diagnosis in 1889, in the fourth edition of the "Manual of Picot and D'Espine," and that Professor Brouardel, in a communication made for him at the session of the Academy of November 8, 1904, said: "The first signs of bronchial adenopathy are furnished exclusively by the *auscultation of the voice,* and are found almost always in the immediate neighborhood of the vertebral column between the seventh cervical vertebra and the first dorsal vertebra, sometimes in the fossa "sus-épineuse," sometimes in the interscapular space. They consist in a quality (timbre) added to the voice, which may be called *whispering* (*chuchotement*) in the first stage and *bronchophony* in a more advanced stage." He then goes on to say that "it is most important to distinguish the exaggerated normal voice sound from the bronchial voice sound. He says that "the tracheal sound is heard normally through the seventh cervical

* Submitted for publication Feb. 7, 1916.
* Read at the meeting of the New England Pediatric Society, Feb. 4, 1916.

1. D'Espine: Bull. de l'Acad. de méd., Paris, 1907, Series 3, lvii, 167; British Med. Jour., 1910, ii, 1136.

spine, where it ceases abruptly. In bronchial adenopathy the bronchial sound extends downward into the space between the seventh cervical and the fourth or fifth dorsal spines. This space corresponds to the last portion of the trachea and the bifurcation of the bronchi, which is at the level of the third dorsal vertebra." He recommends the use of 333, in French, for making the test, and says, "if auscultation of the loud voice or cry gives no result, the child should be made to speak in a low voice." A sound is then heard which he designates as "whispering (*chuchotement*)." "This sound has the same value as bronchophony."

TABLE 1.—SHOWING PRESENCE OR ABSENCE OF D'ESPINE'S SIGN AT VARIOUS AGES

Age, Years	Present	Absent	Total	Per Cent.
1- 2	1	63	64	1.6
2- 3	1	79	80	1.3
3- 4	1	59	60	1.7
4- 5	1	83	84	1.2
5- 6	5	91	96	5.2
6- 7	5	68	73	6.8
7- 8	9	70	79	11.4
8- 9	9	42	51	17.6
9-10	3	20	23	13.0
10-11	4	33	37	10.8
11-12	1	18	19	5.3
	40	626	666	6.0

In a later communication in the *British Medical Journal* of 1910, he says that "the sign is most obvious when the child is made to speak or count in a low voice. The voice is then accompanied by an added whispering sound localized to one or two vertebrae, or possibly extending to the fourth or fifth. A bronchial quality to the respiration at the same place has the same diagnostic value as the whispered sound. It is necessary to be content with this, if the child is too young to speak, but the bronchial breathing is a sign of enlargement already more considerable and more extensive. It is the same with vertebral percussion."

Having read only D'Espine's articles when I began to test for the presence of this sign, I naturally took for the line dividing the normal from the abnormal, the line between the seventh cervical and first

TABLE 2.—Data Concerning D'Espine's Sign

Age, Yrs.	Location	Remarks
1¾	5 D	Tuberculin test positive.
2¼	?	Typhoid fever; father perhaps tuberculous.
3½	?	Asthma.
4	3 D	Adenoids.
5	4 D	Frequent "colds"; sign gone 2½ years later.
5½	4 D	Asthma.
5⅔	?	Tuberculosis of knee.
5¾	?	Just over bronchopneumonia.
5¾	4 D	Chronic bronchitis; influenza bacilli found.
6	4 D	"Below par"; normal otherwise.
6	5 D	Acute bronchitis.
6½	5 D	Bronchitis; gone seven months and three years later.
6½	4 D	Just over pertussis; had tuberculous glands in neck two years before.
6⅔	?	Delicate child; known exposure to tuberculosis.
7	5 D	Acute endocarditis.
7	?	Epilepsy.
7	3 D	Recurrent bronchitis.
7⅛	4 D	Chronic valvular disease; sign absent five months before.
7½	?	Just over "cold"; absent two years before.
7½	4 D	Chronic bronchitis; no tubercle bacilli in sputum; tuberculin test neg.
7½	?	Bronchopneumonia.
7½	?	"Cold" for four weeks.
7¾	?	Feebleminded.
8	3 D	Delicate child; recurrent bronchitis.
8	3 D	Bronchitis and asthma.
8	4 D	Acute bronchitis
8	3 D	Habit spasms.
8¼	?	Cervical adenitis, probably tuberculous.
8¼	?	Delicate child.
8¼	?	Known exposure to tuberculous milk.
8½	4 D	Bronchitis and asthma; tuberculin test positive.
8½	?	Masturbation; sign present two years later, but child very well.
9	?	Acute yellow atrophy of liver.
9	4 D	No disease.
9½	?	Adenoids and large tonsils.
10	1 D	Tuberculosis of lungs and cervical glands.
10½	2 D	Chorea.
10½	?	Hysteria; tuberculin test positive.
10⅔	3 D	Delicate child; functional heart disease.
11	4 D	Delicate child.

dorsal spines. Both the whispered voice and the spoken voice were used in making the tests. In some cases one was more satisfactory, in others, the other. In rare instances, in the younger children, the cry was used. No conclusions were drawn from the character of the respiration alone. In 626 of the 666 children, or 94 per cent., the change in the voice sound occurred between the seventh cervical and the first dorsal spines. These figures seem sufficient to prove that in childhood D'Espine's original contention as to the location of the normal change in sound is correct. They also seem to show that those who state that the change in sound normally occurs at the second dorsal spine or, as some say, at the fourth dorsal spine, are wrong in their statements.

The fact that D'Espine's sign was present in but forty of 666 children, or only 6 per cent., shows that D'Espine's sign is uncommon in the children of the wealthy and well-to-do classes of our community. The accompanying table (Table 1) shows that D'Espine's sign is very seldom present in these children before 5 years, that it is most common between 8 and 9 years, and that its frequency diminishes from that time on.

Table 2 shows the ages at which the sign was found, the location of the change in sound when it was specified in the notes, and such other data as seem of importance.

It is, of course, impossible to analyze such a table accurately. It would seem, however, that in eighteen, or nearly 50 per cent., of the children the enlargement was probably not tuberculous. In nine it probably was tuberculous, and in thirteen there is no data pointing either one way or the other. These figures show what is now generally accepted, namely, that D'Espine was wrong in his conception that his sign was always a manifestation of tuberculosis of the bronchial glands. The presence of this sign means merely that there is some tissue between the trachea and bronchi and the vertebral column which transmits the bronchial sound unchanged, whereas under normal conditions it is modified during its transmission. This tissue is ordinarily made up of the enlarged tracheobronchial lymph nodes. The enlargement of these nodes may or may not be due to tuberculosis. These figures also seem to show that among the well-to-do-classes enlargement of the tracheobronchial lymph nodes is almost, if not quite, as often non-tuberculous as tuberculous. Too much importance cannot be attached to them, however, because positive proof as to the nature of an enlargement of these nodes can be furnished only by necropsy. It is especially noticeable how frequently they are enlarged in asthma with chronic bronchitis.

CONCLUSIONS

The following conclusions seem warranted from the study of these cases:

D'Espine was correct in his original contention that the normal change in the voice occurs between the seventh cervical and the first dorsal spines.

D'Espine's sign is present, therefore, when the bronchial voice, or whisper, is heard below the seventh cervical spine.

D'Espine's sign is uncommon in children of the well-to-do classes. When it is present in them, it is probably not a manifestation of tuberculosis in more than 50 per cent.

70 Bay State Road.

ACROCEPHALOSYNDACTYLISM—A TERATOLOGICAL TYPE *

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Acrocephalosyndactylie (Apert), acrosphenodactylie (Maygrier) or acrocephalosyndactylism, was first described by Troquart[1] in 1886. Since the first description there have been ten other cases noted, namely, those of Beno[2] in 1886, Galippe and Magnan[3] in 1892, Wheaton,[4] two cases, in 1894, Dubrisay[5] in 1898, Maygrier[6] in 1898, Fournier[7] in 1898, Camus[8] in 1905, Davis[9] in 1915, and Bertolotti and Boidi-Trotti[10] in 1915. Two other cases of symmetrical syndactylism with pathological changes in the bones of the head have been described but the descriptions are not of sufficient exactness to allow a diagnosis to be made. These cases are those of Parham[11] and Haultain.[12]

Apert,[13] in 1906, described the condition at length, and later Sterling,[14] in 1914, in a review of the trophic diseases, deformities and delayed development of the osseous system, collected and reported cases to date and discussed the principal characteristics, which are as follows: The cranium shows a marked lengthening in the external distance from the nasion to the inion. The anteroposterior diameter is greatly shortened. The superciliary ridges are highly arched and flattened and the brow bulging. The orbits are also flattened anteroposterially, which, together with the deformity of the supercilliary ridges,

* Submitted for publication Jan. 29, 1916.

* From The Babies' Dispensary and Hospital and the Pediatric Department of Western Reserve Medical School.

1. Troquart: Bull. et. mém. Soc. de chir. de Bordeaux, 1886, p. 69.
2. Beno: Thèse de Nancy, 1886, Observation xxix.
3. Galippe and Magnan: Compt. rend. Soc. de biol., 1892, Series 9, iv, Part 2, p. 277.
4. Wheaton: Tr. Path. Soc. London, 1894, xlv, 238.
5. Dubrisay: Bull. Soc. d'obst. de Paris, 1898, i, 81.
6. Maygrier: Bull. Soc. d'obst. de Paris, 1898, p. 28.
7. Fournier, E.: Thèse de Paris, 1898, Observation cccxxvii.
8. Camus: Bull. Soc. de biol., 1905, p. 1555.
9. Davis, B. F.: Acrocephalosyndactylism, Am. Jour. Dis. Child., ix, 446; Jour. Nerv. and Ment. Dis., 1915, xlii, 567.
10. Bertolotti and Boidi-Trotti: Riforma med., 1915, xxxi, 679. Boidi-Trotti: Gior. d. r. Accad. di med. di Torino, 1915, Series 4, xxi, 123.
11. Paraham: New Orleans Med. and Surg. Jour., 1886, New Series, 7, xiv, 755.
12. Haultain: Edinburgh Med. Jour., 1895, xl, 658.
13. Apert: Bull. et mém. Soc. méd. d. hôp. de Paris, 1906; Series 3, xxiii, 1310.
14. Sterling: Ztschr. f. d. ges. Neurol. u. Psychiat., 1914, ix, 138.

causes a marked proptosis. There is not infrequently found a sulcus or ridge in the situation of the metopic suture. In general the head is symmetrical but in the case of Maygrier[6] and Gallippe[3] it was asymmetrical. The facial bones are profoundly altered. The zygomata are very prominent, the root of the nose depressed (saddle nose), the superior maxillae atrophic, causing the right and left alveolar borders to be pressed together, thereby forming one of the most characteristic features, namely, the very highly arched palate. In fact, this is sometimes so narrow as to give the appearance of a cleft. In those patients that have lived to a sufficient age there has been anomalous dentition. The neck, chest and abdomen show no pathologic changes. The extremities are markedly deformed by the presence of a more or less complete syndactylism. The hands are often in a position of the *main d'accoucheur*. They have been described as "spatula form." They are semi-flexed, and the palms are immobile. The thumbs are mobile and generally not involved in the syndactylism. In only one case were there separate nails. In the other cases they show more or less fusion. Various kinds of anomalous ossification have been mentioned. Probably the most constant deformity has been the fusion of the fourth and fifth metacarpals at their bases. Reduction (oligodactylism) and increase (polydactylism) in the number of the phalanges have been described, as well as the absence of the terminal phalanges (bradydactylism). The feet show anomalies similar to those in hand. Wheaton[4] and Dubrisay[6] report necropsies on their patients. They report the anteroposterior cranial measurements decreased, in one case the basio-occipital bone atrophic, in one premature synostosis of the tribasilar bone, and in one of Wheaton's cases the metopic suture ossified with Wormian bones. In the skull they found other supernumerary bones. The brain showed considerable compression. There were no visceral changes.

Bilateral optic neuritis has been found on opthalmoscopic examination (Fournier[7]) and also some impairment of hearing.

Roentgenographic studies have been made in six cases—Fournier,[7] Maygrier,[6] Dubrisay,[5] Davis,[9] Bertolotti,[10] and in our own case.

The condition is compatible with life. The ages of the described patients vary from new-born babies (Dubrisay[5] and Fournier[7]) to 31 years, as in the case of Galippe and Magnan.[3] The mental activity varies, but in most cases it is stated to be normal.

CASE REPORT

The following case shows all of the characteristic deformities:

History.—Patient R. Z., boy, aged 6 months, was admitted to The Babies' Dispensary and Hospital, Cleveland, with a complaint of "cold in the head."

Family History.—Mother living but has not been well since her first child was born. She has had much pain in the lower abdomen and has worn a pessary to relieve a prolapsus uteri which followed her first pregnancy. There are two other children living and well. No miscarriages. No history of tuberculosis, lues or abnormality in the development of any other member of the family. The father is in good health. The parents attribute the deformity of the patient to a gas explosion which occurred when the mother was four months pregnant.

Personal History.—Birth weight 8 pounds; full term; normal delivery by physician; resuscitation difficult. The infant was breast fed for two weeks after which he was fed irregularly on a simple milk dilution. The child was weaned because of the difficulty in breathing when on the breast. With the exception of numerous "colds in the head" the child has been perfectly well.

Fig. 1.—Enlarged veins of the scalp.

Present Illness.—For three months the child has had an increasing difficulty in breathing, accompanied by a considerable discharge of a mucous substance from the nose.

Physical Examination.—A well nourished baby of 6 months, showing numerous abnormalities in development, especially in the cranium and extremities. The turgor is normal; color of the mucous membranes good; mentality seems normal; smiles, and attention is easily distractable by sounds and light; attempts to grasp objects offered. The superficial lymph glands are of normal size.

The head presents numerous deviations from the normal, the most marked of these being the greatly increased measurement from the nasion to the inion, the pronounced bulging of the forehead, associated with a flattening of the superciliary ridges, the decreased biparietal and anteroposterior diameters, the proptosis, the depressed bridge of the nose and the marked narrowing and high arching of the hard palate. There are slight increases in the bizygomatic

and bitemporal diameters. In the anterior view the head forms a roughly triangular figure when the bizygomatic line is taken as the base and the bregma as the apex. Just above the superciliary ridges there is a marked depression in the frontal bone, giving a sulcus-like formation. This can be seen in Figure 1. The occipital region is greatly flattened. The external occipital protuberance is absent. As will be seen from the following measurements, the deformity is even greater than is apparent from the photographs:

Diameter	cm.
Fronto-occipital	11.
Bitemporal	11.5
Biparietal	10.5
Frontomental	16.5
Bizygomatic	12.0
Transorbital	8.0
Mento-occipital	18.0
Bregma-inion	13.5
Tragus-to-tragus	11.0
Height of orbit	2.75

Circumference	cm.
Fronto-occipital	38.0
Occipitomental	49.0
Lambda and supraorbital	37.5
Lambda-glabella (horizontal)	37.0
Lambda-glabella (vertical)	21.0
Glabella to bregma (vertical)	7.75

Total length of child 66.5 cm.

The anterior and posterior fontanels are open, and the coronal, sagittal and lambdoid sutures are not completely closed. The metopic suture is replaced by a ridge-like bony prominence. The roentgenogram of the head shows the presence of digital impressions in the frontoparietal region.

All the superficial veins of the scalp are greatly dilated. The temporal vein is so greatly dilated as to appear almost a sinus, and it is pulsatile.

The ears are very large and the external auditory canal is compressed anteroposteriorly, giving it a triangular shape and rendering examination of the tympanic membrane impossible. The hearing is apparently acute.

The eyes show a marked proptosis (Fig. 2). The pupils are equal in size and regular in outline. The eyelids are thickened. The outer canthus is considerably lower than the inner.

The nose is markedly depressed at the root, giving it a typical "saddle nose" appearance.

The mouth is constantly open. The tongue is somewhat larger than normal, but it appears even more so on account of its constant protrusion, caused by the short distance between the alveolar border and the postpharyngeal wall.

The hard palate is distinctly deformed. The transverse distance between the alveolar borders is considerably shortened. The palate seems to have been compressed to such a degree as to form a very acute angle. Running from before backward, this forms a narrow but deep sulcus until a short distance in front of the junction of the hard and soft palate, where it opens out laterally. The uvula is normal.

The neck, chest and abdomen are normal.

The hands show a complete syndactylism of all the fingers except the thumbs (Fig. 3-B).

Both hands are in a partially flexed condition, the angle of flexion being mainly between the metacarpals and the proximal phalanges. The thumbs are sharply flexed and adducted. The palms are of the so-called "spoon shape" (Fig. 3-B). The nails are completely fused, although some suggestion of division occurs between the second and third and between the third and fourth. The nail of the thumb is wide and heavy.

The roentgenogram of the right hand (Fig. 4) shows an absence of all the terminal phalanges, unless the break in the shadow of the second digit be interpreted as a joint. In that case it is present in this finger, but there is marked shortening of the second phalanx. The metacarpal bones are not fused There is considerable ossification in the unciform and os magnum.

The roentgenogram of the left hand (Fig. 5) shows the same as the right, with the exception of a fusion of the bases of the fourth and fifth metacarpal bones.

The feet show a complete syndactylism which includes the great toe (Figs. 3-A and 6). They seem shorter than normal. The nails are not fused as much as in the hands. On the left foot those of the great and second toes are completely fused while the others are separate. On the right foot those of the great and first and those of the fourth and fifth toes are partly fused.

Fig. 2.—Characteristic position of tongue and mouth. Proptosis.

The roentgenogram of the left foot (Fig. 7) shows an absence of the terminal phalanges. The first phalanx is much larger than normal. Near the base of the second there is a large sesamoid bone. The first and second metatarsal bones are connected near their bases.

The roentgenogram of the right foot (Fig. 8) shows an absence of the terminal phalanges. The first phalanx is larger than normal and on its inner side there is a small notch. At the base of the second metatarsal bone on its outer surface there is a large tuberosity. The remaining metatarsal bones are rather smaller than normal and not as regular as usual.

Fig. 3.—Left foot and right hand.

Fig. 4.—Roentgenogram of right hand.

Fig. 5.—Roentgenogram of left hand.

Fig. 6.—Feet, showing some fusion of nails and bradydactylism.

The occurrence of anomalies and deformities in the various forms of animal life has given rise to an immense amount of speculation as to their causation, but not until recent years has real scientific investigation been attempted to furnish a solution to these most interesting phenomena. For many years in the scientific world maternal impressions were considered as playing a fundamental part in their production, and today the laity still hold to this view. Of late years, however, numerous observers have studied the problem from a much more critical standpoint and a number of experimental attempts at the solution have been made. Stockard[15] obtained quite constant results from breeding animals whose ancestors had been exposed to long periods of intoxication from inhalation of alcohol fumes. He found more congenital

Fig. 7.—Roentgenogram of left foot.

defects of the eyes in the third generation than in the second. Werber,[16] by subjecting the eggs of the marine teleost fish *Fundulus heteroclitus* to butyric acid and acetone, these substances being selected because they are known to arise in various conditions of faulty metabolism in man, obtained such defects as hydrocephalus, cyclopia, and circulatory and ear vesicle defects. Hertwig[17] concluded from his researches that defective development, such as spina bifida in amphibians, could be produced by subjecting fertilized ova to a 0.6 to 0.7 per cent. sodium chlorid solution. He, therefore, suggests that possibly certain monstrous formations in human beings may be due to the presence of certain poisons such as alcohol or toxins in the blood of the mother. Other recent researches by Fere and McClendon in experimental tera-

15. Stockard, C. R.: Arch. f. Entwcklngsmechn. d. Organ., 1912, xxxv, 569; THE ARCHIVES INT. MED., 1912, x, 369.
16. Werber, E. I.: Bull. Johns Hopkins Hosp., 1915, xxvi, 226.
17. Hertwig, O.: Gegenbauer's Festchrift, 1896, ii.

tology have demonstrated that various physical and chemical means can be used to cause defective or monstrous development.

Mall,[18] after a study of 163 pathologic human embryos, believed that the defective development of these embryos was due to a condition which he was pleased to term faulty implantation of the ovum in the wall of the uterus. This is due not to a pathologic condition of the fertilized ovum, but to a diseased condition of the uterine wall. He concluded that from such a diseased condition of the uterine wall the adequate nutrition of the embryo would be impossible and the early death of the embryo from inanition probable. This may well explain

Fig. 8.—Roentgenogram of right foot.

the monstrous condition of those embryos which are aborted early, and even explain defective prenatal development in some of those embryos which survive.

Various other intra-uterine conditions have been advanced as the etiologic factors concerned in defective atypical developments of the ovum, such as hydramnios and oligohydramnios. Wheaton, in 1894, declared that he believed that hydramnios due to syphilis was the cause of the deformity in his cases of acrocephalyosyndactylism.

The various infectious diseases have been pointed out as the etiologic factor in not a few cases of monstrous development, syphilis and tuberculosis, of course, being the diseases most commonly indicated.

18. Mall, F. P.: Jour. Morphol., 1908, xix, 1-367.

One of the most attractive theories for the explanation of certain forms of atypical development is that expounded by Babes[19] in 1904, and by Apert and Babes. They observed that in certain types of cranial deformity there was frequently an associated maldevelopment of the extremities and this association was of such frequency as to cause Apert and Babes[20] to say "A trophic correlation between the base of the brain and the development of the extremities may be presumed."

Babes[21] says further:

> A primary, deep-reaching anomaly of the face, and especially of the base of the skull, had led to an extensive modification of the four extremities. . . . . Without discussing this further at present, intending to come come back to it later, I believe it can be regarded as established that extensive modifications of all the extremities, which I will call *Acrometagenesen*, in consequence, in part, of pathologic changes of a certain region of the anterior base of the skull and in the upper half of the face, may occur, and these modifications are capable of throwing much light into many dark fields in the study of the origin of races and species.

That there is a trophic correlation between the base of the brain or the base of the skull and the development of the extremities is a point which would be difficult to prove by exact methods. From clinical observation, however, the fact that in numerous cases of premature fetal synostosis of the bones at the base of the skull there occur also defects in the development of the extremities, makes the theory of Babes an attractive one.

The cause or causes of the premature synostosis would still be unexplained even were this theory proved.

The regularity of the malformation, as shown by the eleven reported cases of acrocephalosyndactylism, the symmetry of the lesions and their widespread character would seem to disprove the theory of any local damage such as irregularity in the amount of amniotic fluid, for in such a case the deformities are always irregular and asymmetrical.

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19. Babes, V.: Berl. klin. Wchnschr., 1904, xli, 464.

20. Eine tropische Korrelation zwichen Gehirnbasis und der Entwicklung der Extremitaten vermuten.

21. Eine primäre tiefgreifende Anomalies des Gesichtes und besonders der Schädelbasis zu einer tiefgreifenden Umwandlung der vier Extremitaten geführt hatte.

Ohne auf diese Frage näher einzugeben, auf welche zerückzukommen ich mir vorbehalfte, glaube ich als feststehend constatiren zu können, dass sich tiefgreifende Umwandlungen aller Extremitaten, welche ich "Acrometagenesen" nennen will, in Folge von zum Teil pathologischen Veränderungen einer bestimmten Region an der vorderen Schädelbasis und an der oberen Gesichtshälfte vollziehen können, welche Umwandlungen im Stande sind, uber manche dunkle Gebiet ein der Forschung über die Entstehung des Rassen und Arten etwas mehr Licht zu verbreiten.

ON THE PRESENCE OF KETONES AND BETAHYDROXYBUTYRIC ACID IN THE URINE OF NORMAL CHILDREN *

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As a part of general study of the urine of normal children under different dietetic conditions, a number of urines were studied to determine whether or not ketones and betahydroxybutyric acid were present, and if so, in what quantities. Although discussions of acidosis in childhood, and particularly of pathological conditions in which large amounts of "acetone bodies" appear in the urine are numerous, there are no figures in literature, so far as we know, in regard to the amount of these substances in the urine of "normal" or healthy children.

The method used for determining their presence was that of Shaffer, in which the acetone and the aceto-acetic acid are first distilled over, and then the betahydroxybutyric acid oxidized by potassium bichromate and distilled over as acetone. The amount of acetone is then determined by the iodimetric method of Messinger. The children from whom the twenty-four-hour specimens examined were obtained were what is usually termed "normal" with a few exceptions. In a few instances children with fully compensated chronic valvular cardiac disease were utilized, and likewise a few boys with hernias before operation. From the standpoint of their metabolism they may be regarded as normal. The diet was what we term "standard metabolic diet," whose composition will be described in a later paper. It varies for different age periods, contains fat, carbohydrate and protein in proper proportions, and is of sufficient caloric value to cover the needs of children at light work or play. The children were in bed and had been on the diet for several days before the twenty-four-hour specimen used was collected. During this time the temperature was taken frequently in order to be sure that the children were afebrile.

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In the accompanying table the results obtained from the examination of the urines of twenty-one children are tabulated. As the results were so uniform and consistent, it did not seem probable that anything further was to be gained from the study of a larger number of children. The amount of betahydroxybutyric acid is in terms of acetone.

TABLE SHOWING THE PRESENCE OF KETONES AND BETAHYDROXYBUTYRIC ACID IN THE URINES OF TWENTY-ONE NORMAL CHILDREN

Name	Sex	Condition	Age	Weight, Pounds	Acetone and Diacetic Acid	Beta-hy-droxy-butyric	Diet
B. Z.	M.	Normal.....	2 mos.	8½	0.011	0.022	Standard infant
E. B.	M.	Normal.....	14 mos.	25	0.037	0.012	Standard infant
R. K.	M.	Normal.....	19 mos.	26	0.030	0.017	Standard infant
W. C.	M.	Normal.....	21 mos.	22	0.015	0.020	Standard 20 to 36 mos.
A. C.	F.	Normal.....	24 mos.	28	0.010	0.022	Standard 20 to 36 mos.
J A.	M.	Normal.....	28 mos.	24	0.040	0.041	Standard 20 to 36 mos.
P. D.	M.	Oldanterior polio-myelitis	28 mos.	25	0.025	0.017	House diet
C. H.	M.	Normal.....	3 yrs.	27	0.019 0.031	0.035 0.040	Standard 3 to 6 yrs. Three weeks later
A. E.	M.	Normal.....	4 yrs.	35	0.011	0.003	Standard 3 to 6 yrs.
V. R.	F.	Healed eczema....	4 yrs.	35	0.010	0.025	Standard 3 to 6 yrs.
E. F.	M.	Normal.....	5 yrs.	40	0.017	0.029	Standard 3 to 6 yrs.
E. B.	M.	Mental deficiency backward development	5 yrs.	30	0.015	0.018	Standard 3 to 6 yrs.
L. C.	M.	Chr. valvulitis....	7 yrs.	..	0.007	0.030	Standard 6 to 10 yrs.
I. H.	F.	Chr. valvulitis....	8 yrs.	38	0.110 0.090	0.066 0.057	Creatin-free Following day
M. R.	F.	Chr. valvulitis....	9 yrs.	41	0.045	0.037	Standard 6 to 10 yrs.
W. B.	M.	Mental deficiency	9 yrs.	63	0.014 0.030	0.053 0.053	Creatin-free Following day
C. H.	M.	Hernia..... ...	9 yrs.	58	0.033	0.032	Standard 6 to 10 yrs.
C. F.	M.	Hernia.....	10 yrs.	..	0.012	0.020	Standard 6 to 10 yrs.
E. H.	F.	Chr. valvulitis....	10 yrs.	58	0.015	0.044	Standard 6 to 10 yrs.
L. M.	M.	Latent hereditary syphilis	11 yrs.	70	0.015 0.021	0.026 0.035	Standard 10 to 14 yrs. Three days later
T. H.	M.	Hernia.....	12 yrs.	81	0.015	0.022	Standard 10 to 14 yrs.

SUMMARY

It will be noted that small amounts of ketones and betahydroxybutyric were always found in the urines of these normal children when their caloric requirements were fully covered by the diet. The amount was small and varied from 20 to 100 mg. in terms of acetone in twenty-four hours. The average amount excreted was from 50 to 80 mg.

The age, sex, and body weight of the child apparently had no effect on the amount. As a rule the amount of betahydroxybutyric acid was somewhat greater than the amount of ketones, but this did not always hold true. We must regard these substances as present in small amounts in the urine of normal children. The large quantity of "acetone bodies" in the urine in febrile conditions and on restricted diets is due to the increase of substances normally present, rather than to the appearance of abnormal substances.

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THE SECRETION OF BILE IN ICTERUS NEONATORUM *

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About four years ago I undertook a study of icterus neonatorum by means of the duodenal catheter,[1] for it seemed as if a method of obtaining bile at the site of entry into the intestine offered advantages over methods hitherto employed. Accordingly a considerable number of infants, some 124 in all, were tested by this means, and observations were made as to the onset of the excretion of bile in the new-born, its relation to the intake of colostrum, and especially as to its association with jaundice. The details of the various cases comprising this investigation will be found in the paper referred to. The results may be broadly summarized in a short table (Table 1).

In order to determine the onset of the excretion of bile, tests were carried out day after day for a period of several days on each infant, the aspiration being continued for two ten-minute periods. First, a number of unselected infants were examined, and later a group chosen on account of early or marked icterus. The conclusions drawn from these tests were: that bile is very rarely excreted during the first twelve hours of life; that its secretion in the subsequent days is variable, being more profuse in cases with marked jaundice; that when jaundice manifests itself, it precedes the excretion of bile into the duodenum; that secretion varies within wide limits; and that the occurrence of jaundice results from a defective correlation of excretion and secretion, it being generally caused by the inability of the rudimentary excretion to cope with the sudden profuse secretion of bile.

About a year after the publication of this paper, Ylppö[2] published a most interesting article on this subject, regarded from an entirely new point of view. He carried out spectrophotometric examinations of the blood, urine and stools in icterus neonatorum, and in this way determined the amount of bile pigments which they contained. His conclusions relating to the occurrence of bile in the stools may be summarized as follows: first, that there is an increased secretion of bile after birth, augmenting gradually during the first five "critical days" until about the sixth day, when there is again a marked rise in the volume of bile secreted; second, that there is no difference between the icteric and the

* Submitted for publication Feb. 4, 1916.

1. Hess, A. F.: Am. Jour. Dis. Child., May, 1912, p. 304.
2. Ylppö, A.: Ztschr. f. Kinderh., 1913, Orig., ix, 208.

nonicteric infant in the amount of secretion or excretion of bile. Ylppö has represented in the form of curves the gradual rise during the first five days of life, as well as the sudden rise occurring at the end of this period; five curves of this kind are depicted, based on the examinations of eleven infants.

These conclusions—the definite curve of secretion and excretion, as well as the relation of bile excretion to icterus—are, it will be noted, in conflict with the results previously obtained by me, and it is for this reason that I have returned to this subject, especially as this paper has been reviewed in a recent number of this journal.[3] During the past two years, in view of Ylppö's statements, I have availed myself of numerous opportunities to repeat these tests of the new-born, and have obtained the same results as before and been led to the same conclusions.

TABLE 1.—Relation of Age to Excretion of Bile (Duodenal Catheter)

No. of Cases	Age	No Bile	Bile	Marked Jaundice	Remarks
52	½ to 12 hours.....	51	1	0	Thirty-nine infants were less than 6 hours old.
19	12 to 36 hours.....	15	4	4	Marked jaundice in all four positive cases; in others no bile obtained.
15	1½ to 3 days.....	5	10	6	Marked jaundice in four positive cases; in other two jaundiced cases, bile next day.
13	3 to 4 days.....	4	9	6	Jaundice not increasing.
12	4 to 5 days.....	2	10	5	Jaundice decreasing.
13	6 to 11 days.....	2	11	4	Jaundice decreasing.

Before entering into an analysis of the data, in order to attempt to explain the conflicting opinions, we must realize that examinations of the stool furnish merely an indirect method of determining excretion of bile, and that they presuppose something which is by no means certain, namely, that no bile is reabsorbed by the intestine. Tests by means of the duodenal catheter, on the other hand, are not open to this criticism.

At the very outset let me say that I believe it is not possible to construct a reliable curve representing bile excretion in the new-born, and that I relinquished as fruitless such an attempt at the time of writing the previous article. If the degree of secretion were to be depicted graphically, it would not constitute a gradually rising curve, but an irregular and precipitous marking, for the secretion during the first

3. Holmes, J. B.: Am. Jour. Dis. Child., January, 1916, p. 62.

twelve or twenty-four hours is very scant indeed, and generally increases rapidly during the next few days. But graphic illustration is absolutely inapplicable to this study, as in one case there may be an intense secretion of bile by the second day of life, and in others practically none until the fifth or sixth day. Reference to the tests previously reported would seem convincing on this point, for they show all manner of variations in the rate of excretion. How, then, does it come about that Ylppö described a gradually increasing wave of secretion, with a sudden exacerbation about the fifth day? This lay in the very method by which he approached the problem. At the outset he formulated four periods, the first embracing the first five days of life, the second the sixth to the eighth day, the third from the ninth to the eleventh day, and the fourth the twelfth and thirteenth days. As he found a decidedly greater amount of bile in the stool passed during the second period, which, we will remember, began with the fifth day, than that passed during the first period, he drew the conclusion that a sudden flow of bile occurred on about this day, and outlined a hypothetical curve to represent a gradually increasing secretion throughout the first period. It is evidently impossible, as has been pointed out elsewhere,[4] to construct a curve of daily excretion by determining the bile in the total stool passed during these several periods, or to form any opinion whatsoever as to the degree of secretion or excretion for the individual twenty-four periods during the first five days of life. Nor is it possible to state that there is a sudden rise taking place at the fifth or sixth day. This method evidently allows one merely to compare the four periods one with another. Daily tests carried out by means of the duodenal catheter, however, have led me to the opinion that there is an initial lack of excretion during the first twenty-four hours or more, and that there follows a somewhat sudden rise in the outflow of bile, this increase taking place generally before the fifth day, frequently on the third or fourth day.

The second question for consideration is whether there is an increased excretion of bile more often in infants showing decided icterus than among those who manifest no signs of jaundice. Ylppö answers this in the negative. His conclusions are based on a study of ten cases, in which the amount of bile pigment was determined in the total stool passed during the first five days. The data of these cases are given in Table 2 and show the grade of icterus, the total amount of bile pigment found, and the total number of grams of stool excreted. It would seem as if ten cases were very few on which to base definite conclusions, especially when these cases must be subdivided so as to represent three clinical groups, one showing no jaundice, another moderate jaundice,

4. Hess, A. F.: Ergeb. d. inn. Med. u. Kinderh., 1914, xiii, 560.

and a third marked or intense jaundice. Furthermore, it will be noted in the table that in two of the three cases in which no jaundice occurred, but in which, nevertheless, a marked excretion of bile took place, the amount of stool obtained during this period was exceptionally large, indeed, two or three times the number of grams collected in many of the other cases. This is difficult to understand, and certainly renders these cases unsuitable for the purpose of comparison, for we should expect to obtain an abnormal amount of bile under such circumstances.

TABLE 2.—Relation of Bile Excretion to Stool Passed During First Five Days of Life. (Ylppö's Cases.)

Case No.	Grade of Icterus	Total Bile in Stool in First Five Days, Mg.	Total Stool, Gm.	Remarks
1	Negative	28.16	16.09	
2	Marked	8.28	3.22	Immense quantity of bile pigment excreted in next two days (57.83 gm.).
3	Moderate	39.79	4.72	
4	Moderate	21.13	2.93	
5	Negative	43.89	5.72	
6	Moderate	29.95	9.63	
7	Negative	32.77	13.42	
8	Very marked	21.70	12.35	
9	Slight	33.85	6.50	
10	Marked	28.84	19.10	

It is quite true that there is no absolute parallelism between bile excretion and jaundice. Cases previously reported illustrate the occasional occurrence of a wide divergence in these respects. For example, we have noted a high degree of jaundice accompanied by an excessive secretion of bile; no secretion of bile, and almost an absence of jaundice during the first five days of life; and an instance showing marked jaundice on the fourth day, but no secretion of bile until two days later. These cases, however, constitute the exceptions. If we examine a hundred or more cases, more particularly if we select a number of infants on account of the occurrence of marked jaundice, we shall find that an excessive excretion of bile is associated more often with a marked than with a faint degree of jaundice. This will be more especially the case if the duodenal tests are carried out between the second and fifth day, when the excretion has been well established and the icterus has begun to recede.[5]

5. It is difficult to conceive how it will be possible to estimate the daily excretion of bile during life by any method other than duodenal tests. The only other possible means of access would seem to be a fistula.

The amount of bile flow and the icterus do not depend on one factor, but on two—secretion and excretion. This is well illustrated by some cases of congenital obliteration of the bile ducts described by Still[6] and also by Thompson,[7] in which, in spite of the absolute obstruction, there was no jaundice for some weeks owing to the lack of secretion. When jaundice is intense, however, the secretion of bile cannot be wanting, and we are more apt to encounter it in plenty in the duodenum than to find it deficient. In cases selected on account of marked jaundice, bile was frequently found in the stomach by means of a stomach tube, or appeared with regurgitated colostrum, owing to the fact that its marked alkalinity tended to a relaxation of the pyloric sphincter. In the most marked case which we met with, in which the infant assumed a saffron color, there was an almost constant welling forth of bile into the stomach.

CONCLUSIONS

In conclusion we may state that the amount of bile-flow during the first twelve to thirty-six hours of life is very scanty, and that, although it then increases in volume, it is subject to wide fluctuations. It is therefore inaccurate to depict it graphically, as has been attempted, as a gradual rise dating from the time of birth. To quote from our previous paper: "The secretion of bile varies within wide limits. In general it is marked when jaundice is marked."

Furthermore, recent investigations of icterus neonatorum seem to confirm the interpretation that "the occurrence of jaundice results from a defective correlation of excretion and secretion, and is generally caused by the inability of the rudimentary excretion to cope with the sudden profuse secretion of bile."

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6. Still, G. F.: Clin. Jour., 1901, xvii, 323.
7. Thompson, J.: Congenital Obliteration of the Bile Ducts, 1902.

CLINICAL DEPARTMENT

A CASE OF SECONDARY HYPERTROPHIC OSTEO-ARTHROPATHY IN A GIRL 11 YEARS OLD*

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Although 144 cases of secondary hypertrophic osteo-arthropathy have been reported, only seven of these occurred in children. The following case, therefore, seems worthy of being reported:

REPORT OF CASE

History.—B. B., aged 11½. There is no history of tuberculosis or syphilis in the family. The parents have been married twenty-two years and have had eight children. The eldest, now 21 years old, is married and has two healthy children. There have been no deaths and the mother has had no miscarriages or stillbirths. None of the other children have had any symptoms pointing to tuberculous or syphilitic disease of the lungs, bones or lymph nodes. The patient was breast fed for one year, began to walk at the age of 1½ years, and had measles at 2 years. She was always weaker than the other children. When she was 7 years old, the mother noticed that she held her head to one side and did not stand straight. At this time she had been associating with a girl in the neighborhood who had hip disease and was wearing a plaster dressing. The spinal curvature became rapidly more marked. In 1912, when 8 years old, she was admitted to the Hospital for the Ruptured and Crippled and a Hibb's operation was performed by Dr. Whitman. At the time of the operation there was no distinct evidence of tuberculosis and no spasm, but only a marked limitation movement, such as was evidently due to the ankylosis and the resulting deformity of the spine. The child improved during the following year, but has grown worse during the last two years. At one time there were symptoms of paraplegia and the patellar reflexes were exaggerated. Roentgenologic examination at the time showed that there was destruction of the bodies of the fifth, sixth and seventh dorsal vertebrae, with very marked deformity of the spine. During the past four years she has lost weight, has had a cough, which is worse at night, but has not had night sweats. The enlargement of the ends of the fingers was first noticed seven months, and that of the knees and ankles about four months, prior to examination, and that of the wrists and joints of the fingers only a few weeks previously. There has been pain, not very severe in the knees, ankles and fingers.

Examination.—The patient was admitted to the Lebanon Hospital, September 1, 1915, at which time she weighed 49 pounds, was poorly nourished, anemic, and had marked curvature of the spine with pronounced deformity of the chest (Fig. 1). The nose appeared large and broad and the jaw prominent. There was dyspnea which became more marked after slight exertion. On account of the deformity of the chest the examination of the lungs was difficult. The heart sounds were normal. There were fine râles heard

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in the axillary line and over both bases posteriorly. The patient complained of pain on both sides of the chest, more intense on coughing or deep inspiration. There was a small quantity of mucopurulent expectoration; large quantities were never present; it was never foul-smelling and examination on two occasions failed to show the presence of the tubercle bacillus. The von Pirquet cutaneous reaction, however, was positive. The Wassermann reaction was negative. There was distinct atrophy of the muscles of the arm (Fig. 1), the wrists were enlarged, the hands were cold but not cyanotic, the joints of the fingers slightly swollen, and the ends distinctly clubbed (Fig. 2). Examination of the abdominal organs presented nothing abnormal. The circumferences of the knee (Fig. 3) and ankle joints were increased and there was some

Fig. 1.—Author's patient, showing broad nose, prominent jaw, deformity of the chest and atrophy of the muscles of the arm.

atrophy of the muscles of the leg. The patient's temperature ranged between 99 and 101.2 F. The urine contained a small amount of albumin but no casts. During her stay in the hospital (two weeks) the patient gained 1 pound.

Roentgenologic examination of the hand (Fig. 4) showed a deposit of a thin layer of newly formed bone under the periosteum of the metacarpals and a similar but less distinct layer in the first phalanges. At the ends of the terminal phalanges small "burr-like" projections were noted. The joints of the fingers and the wrist showed no changes. Similar changes were seen in the metatarsal bones of the foot and the terminal phalanges, especially the last phalanx of the middle toe (Fig. 5). The knee (Fig. 6) showed a similar

subperiosteal deposit over the lower end of the femur and the upper end of the tibia and fibula. No changes in the knee joint itself were noted. Similar deposits of newly formed bone were found over the lower end of the radius and the ulna and the lower portion of the tibia and the fibula.

According to Locke,[1] 144 cases of secondary hypertrophic osteo-arthropathy, including his own, have been reported. Of these only seven occurred in children.[2]

In adults, the condition occurs five times as often in men as in women, and most of the patients are between 20 and 40 years of age. It is always secondary; some form of chronic disease of the lungs is present in 78 per cent. of the cases, the most frequent lesion being bronchiectasis, which is nearly always present in the most marked cases. Pulmonary tuberculosis is present as an etiologic factor in 20 per cent., and empyema is next in frequency. One of the most plausible explanations as to the cause of the changes in the bones and other tissues is that the imperfect function of the lungs causes a lack of proper elimination of toxic substances; these being absorbed into the circulation, cause changes where the circulation is slowest, namely, in the distal parts. Occasionally similar changes follow certain diseases

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1. Locke: Secondary Hypertrophic Osteo-Arthropathy and Its Relation to Simple Club Fingers, with a complete bibliography, Arch. Int. Med., 1915, xv, 659.

2. Bamberger: (Ztschr. f. klin. Med., Berl., 1891, xviii, 193) Boy, aged 7 years; chronic pulmonary tuberculosis; typical findings at postmortem examination. Davis: (Jour. Am. Med. Assn., 1895, xxiv, 845) Boy, aged 4½ years; empyema communicating with a bronchus; typical report. Hall: (Edinburgh Med. Jour., 1905, New Series 18, lx, 127) Boy, aged 14 years; sarcoma of the lung and sarcoma of the femur; typical postmortem findings. Lockwood: (Tr. Clin. Soc. London, 1897, xxx, 133) Girl, aged 10 years; chronic pulmonary tuberculosis; spinal caries; description typical. Rendu and Boulloche: (Bull. et mém. Soc. méd. d. hôp. de Paris, 1901, xviii, 127) Boy, aged 11 years; empyema; attacks of pain and swelling of the joints without rise of temperature; typical roentgenograms. Thompson: (Tr. Med.-Chir. Soc. London, 1904, lxxxvii, 85) Girl, aged 10 years; chronic engorgement of the lung; spondylitis; amyloid disease; typical roentgenograms. Whitman: (Pediatrics, 1899, vii, 154) Girl, aged 8 years; chronic pulmonary tuberculosis, spondylitis, bones tender; typical roentgenograms. To these the following more or less atypical cases may be added: Gilbert and Fournier: (Rev. mens. d. mal. de l'enf., 1895, xiii, 309) Child, aged 13 years; hypertrophic biliary cirrhosis; no disease of the lung; swelling of the bones near the knee; pain in the wrist, clubbing of the fingers. Child, aged 13 years; hypertrophic biliary cirrhosis; no disease of the lungs; enlargement of the ends of the tibia; pain and swelling of the knee; clubbing of the fingers. The following cases showed clubbing of the fingers without changes in the bones: Moizard: (Bull. et mém. Soc. med. d. hôp. de Paris, 1893, x, 359) Boy, aged 6 years; pneumonia and empyema. Girl, aged 5 years; pneumonia and empyema. Marfan: (Bull. et mém. Soc. méd. d. hôp. de Paris, 1893, x, 365) Child with empyema; child with bronchiectasis; child with cystitis and pyelonephritis. Béclère: (Bull. et mém. Soc. d. hôp. de Paris, 1901, xviii, 283) Child with aneurism of the subclavian artery; clubbing of the fingers of one hand; no changes in the bones.

of the liver, the disturbed function of the organ resulting in imperfect elimination. The characteristic feature of the condition is the deposit of a thin layer of new bone under the periosteum, more marked in certain bones, namely, the lower end of the radius and ulna, the lower end of the tibia and fibula, the metacarpals, the metatarsals, and the first

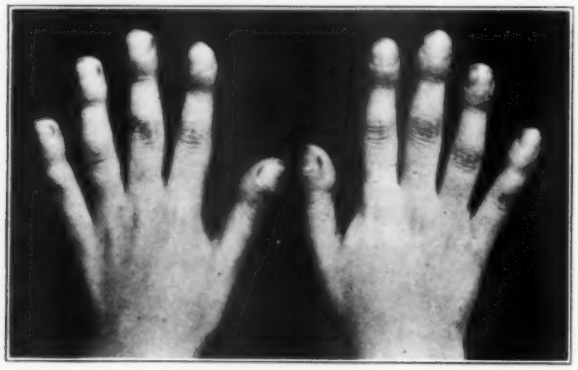

Fig. 2.—Showing clubbing of the fingers and slight swelling of the joints of the fingers.

Fig. 3.—Showing enlargement of the knee joints.

phalanges of the hands and feet; somewhat less distinct in the humerus, femur, upper end of radius, ulna, tibia, fibula, clavicle, acromion process, ribs and iliac crest. A careful roentgenologic study in well-marked cases shows that nearly all the bones are affected. In such cases the epiphyses may also show irregular deposits. This layer of newly

Fig. 4.—Showing deposit of layer of newly formed bone on the metacarpal bones and first phalanges, and burr-like proliferation on the distal half of the terminal phalanges.

Fig. 5.—Showing deposit of layer of newly formed bone on the metatarsal bones and burr-like proliferation on the terminal phalanx of the middle toe.

Fig. 6.—Showing layer of newly formed bone on the lower end of the femur and the upper end of the tibia and fibula. The joint itself is apparently normal.

formed bone which is most distinct at the lower end of the shaft begins a couple of inches above the joint and stops at the edge of the cartilage. According to Locke the process is a slowly progressive ossifying periostitis. At first this periosteal layer is sharply defined, but after a couple of years it has a tendency to fuse with the underlying parts, so that it becomes less distinct. The roentgenologic examination in the late stages shows a decrease in the density of the shaft. The clubbing of the fingers is due largely to changes in the soft parts, but the terminal phalanges frequently show a "burr-like" proliferation in their distal half and occasionally osteophytes (Fig. 4). The joints usually show no changes, but in severe cases there may be thickening of the periarticular tissue, slight effusion, and erosion of the cartilage.

An interesting and important question is the relation of cases of simple clubbing of the fingers to cases of secondary hypertrophic osteo-arthropathy. Locke believes that the conditions are identical, the former representing an early stage of the latter. He bases his opinion primarily on the fact that in a series of thirty-nine cases of simple clubbing, eleven, or 28 per cent., showed, roentgenologically, changes in the long bones similar to those seen in osteo-arthropathy. The fact that 72 per cent. of the cases of simple clubbing are associated with pulmonary disease, and 50 per cent. with pulmonary tuberculosis, is also suggestive. In my own case the clubbing of the fingers was the first manifestation of changes in the extremities.

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